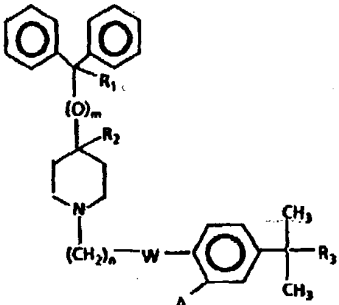


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(54) Title: NOVEL INTERMEDIATES FOR THE PREPARATION OF ANTIHISTAMINIC 4-DIPHENYLMETHYL/DIPHENYLMETHOXY PIPERIDINE DERIVATIVES			
(57) Abstract <p>The present invention is related to novel intermediates and processes which are useful in the preparation of certain antihistaminic piperidine derivatives of formula (I) wherein W represents -C(=O)- or -CH(OH)-; R₁ represents hydrogen or hydroxy; R₂ represents hydrogen; R₁ and R₂ taken together form a second bond between the carbon atoms bearing R₁ and R₂; n is an integer of from 1 to 5; m is an integer 0 or 1; R₃ is -COOH or -COOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched; each of A is hydrogen or hydroxy; and pharmaceutically acceptable salts and individual optical isomers thereof, with the proviso that where R₁ and R₂ are taken together to form a second bond between the carbon atoms bearing R₁ and R₂ or where R₁ represented hydroxy, m is an integer 0.</p>			
 <p style="text-align: right;">(I)</p>			

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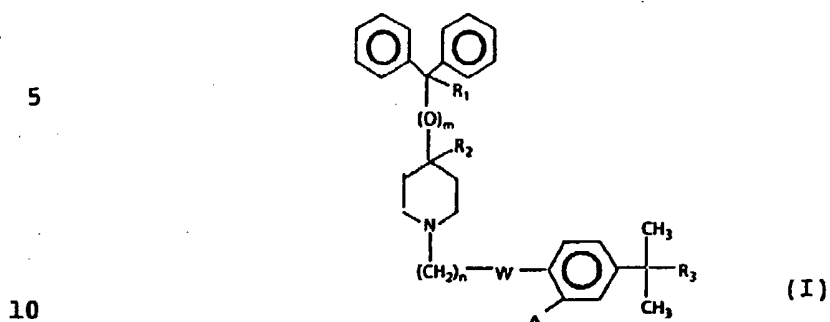
1 NOVEL INTERMEDIATES FOR THE PREPARATION OF ANTIHISTAMINIC 4-
DIPHENYLMETHYL/DIPHENYLMETHOXY PIPERIDINE DERIVATIVES

BACKGROUND OF THE INVENTION

- 15 This is a Continuation-In-Part Application of Patent
Application Serial No.08/144,084, filed October 27, 1993
which is a Continuation-In-Part Application of Patent
Application Serial No. 08/082,693, filed June 25, 1993.
- 20 The present invention is related to novel intermediates
which are useful in the preparation of certain piperidine
derivatives which are useful as antihistamines, antiallergy
agents and bronchodilators [United States Patent No.
4,254,129, March 3, 1981, United States Patent No.
25 4,254,130, March 3, 1981, United States Patent No.
4,285,958, April 25, 1981 and United States Patent No.
4,550,116, Oct. 29, 1985].

These antihistaminic piperidine derivatives can be
30 described by the following formula:

35



wherein

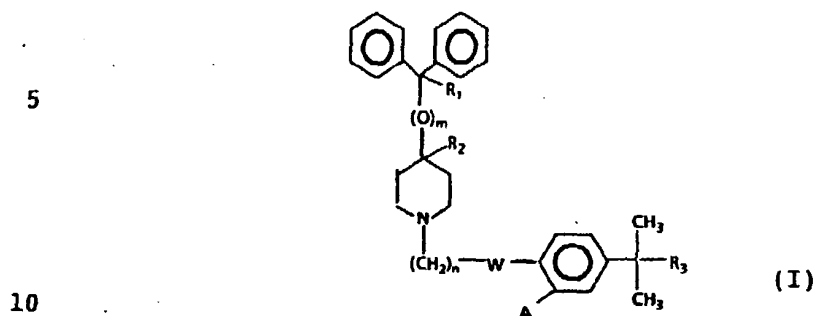
- W represents $-C(=O)-$ or $-CH(OH)-$;
- 15 R_1 represents hydrogen or hydroxy;
- R_2 represents hydrogen;
- R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;
- n is an integer of from 1 to 5;
- 20 m is an integer 0 or 1;
- R_3 is $-COOH$ or $-COOalkyl$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;
- each of A is hydrogen or hydroxy; and
- pharmaceutically acceptable salts and individual
- 25 optical isomers thereof,
- with the proviso that where R_1 and R_2 are taken together to form a second bond between the carbon atoms bearing R_1 and R_2 or where R_1 represented hydroxy, m is an integer 0.

30

SUMMARY OF THE INVENTION

The present invention provides novel intermediates useful for the preparation of certain antihistaminic

35 piperidine derivatives of formula (I)



wherein

W represents -C(=O)- or -CH(OH)-;

15 R₁ represents hydrogen or hydroxy;

R₂ represents hydrogen; or

R₁ and R₂ taken together form a second bond between the carbon atoms bearing R₁ and R₂;

n is an integer of from 1 to 5;

20 m is an integer 0 or 1;

R₃ is -COOH or -COOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;

each of A is hydrogen or hydroxy; and

25 pharmaceutically acceptable salts and individual optical isomers thereof,

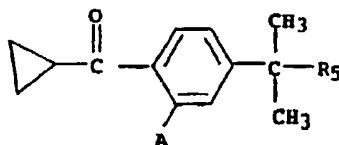
with the proviso that where R₁ and R₂ are taken together to form a second bond between the carbon atoms bearing R₁ and R₂ or where R₁ represented hydroxy, m is an integer 0.

30

These novel intermediates are described by the following formulas:

35

5 (II)



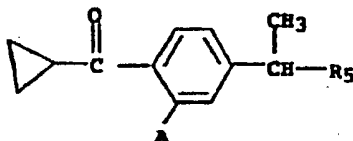
wherein

A is a hydrogen or hydroxy; and

- 10 R₅ is H, -CH₂OD wherein D is hydrogen, acetate or benzoate, -CHO, Br, Cl, I, CN, -COOH, -COOalkyl or -CONR₆R₇ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched and R₆ and R₇ are each independently H, C₁-C₆alkyl, C₁-C₆alkoxy
- 15 or R₆ and R₇ taken together with the nitrogen atom form a pyrrolidine, piperidine or morpholine, with the proviso that R₆ and R₇ cannot both be represented by C₁-C₆alkoxy.

20

(III)



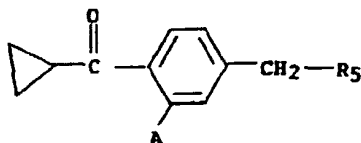
25 wherein

A is a hydrogen or hydroxy; and

- R₅ is H, Br, Cl, I, CN, -COOH, -COOalkyl or -CONR₆R₇ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched and R₆ and R₇ are each independently H, C₁-C₆alkyl, C₁-C₆alkoxy
- 30 or R₆ and R₇ taken together with the nitrogen atom form a pyrrolidine, piperidine or morpholine, with the proviso that R₆ and R₇ cannot both be represented by C₁-C₆alkoxy.

35

5 (IV)



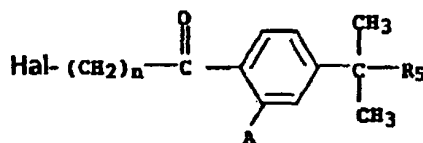
wherein

A is a hydrogen or hydroxy; and

- 10 R₅ is H, Br, Cl, I, CN, -COOH, -COOalkyl or
 -CONR₆R₇, wherein the alkyl moiety has from 1 to 6
 carbon atoms and is straight or branched and R₆ and
 R₇ are each independently H, C₁-C₆alkyl, C₁-C₆alkoxy
 15 or R₆ and R₇ taken together with the nitrogen atom
 form a pyrrolidine, piperidine or morpholine, with
 the proviso that R₆ and R₇ cannot both be
 represented by C₁-C₆alkoxy.

20

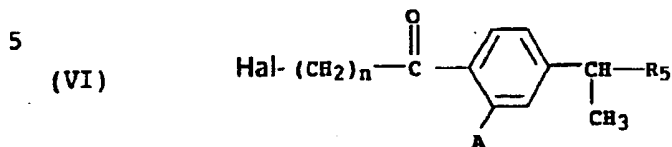
(V)



wherein

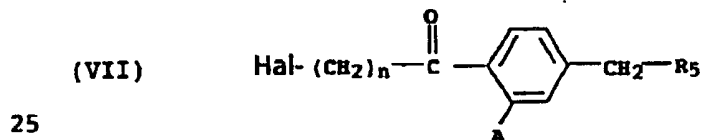
- 25 Hal is Cl, Br or I;
 n is an integer of from 1 to 5;
 A is a hydrogen or hydroxy; and
 R₅ is H, CH₂OD wherein D is hydrogen, acetate or
 benzoate, CHO, Br, Cl, I, CN, -COOH or -CONR₆R₇
 30 wherein R₆ and R₇ are each independently H, C₁-
 C₆alkyl, C₁-C₆alkoxy or R₆ and R₇ taken together with
 the nitrogen atom form a pyrrolidine, piperidine or
 morpholine, with the proviso that R₆ and R₇ cannot
 both be represented by C₁-C₆alkoxy.

35



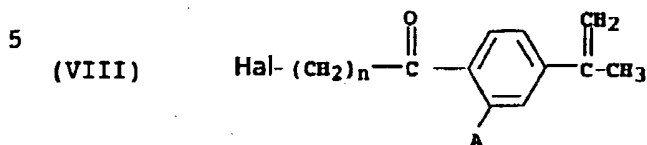
wherein

- 10 Hal is Cl, Br or I;
 n is an integer of from 1 to 5;
 A is a hydrogen or hydroxy; and
 R₅ is H, Br, Cl, I, CN, -COOH, -COOalkyl or
 -CONR₆R₇ wherein the alkyl moiety has from 1 to 6
 15 carbonatoms and is straight or branched and R₆ and
 R₇ are each independently H, C₁-C₆alkyl, C₁-C₆alkoxy
 or R₆ and R₇ taken together with the nitrogen atom
 form a pyrrolidine, piperidine or morpholine, with
 the proviso that R₆ and R₇ cannot both be
 20 represented by C₁-C₆alkoxy.



wherein

- Hal is Cl, Br or I;
 n is an integer of from 1 to 5;
 30 A is a hydrogen or hydroxy;
 R₅ is H, Br, Cl, I, CN, -COOH, -COOalkyl or
 -CONR₆R₇ wherein the alkyl moiety has from 1 to 6
 carbon atoms and is straight or branched and R₆ and
 R₇ are each independently H, C₁-C₆alkyl, C₁-C₆alkoxy
 35 or R₆ and R₇ taken together with the nitrogen atom
 form a pyrrolidine, piperidine or morpholine, with
 the proviso that R₆ and R₇ cannot both be
 represented by C₁-C₆alkoxy.

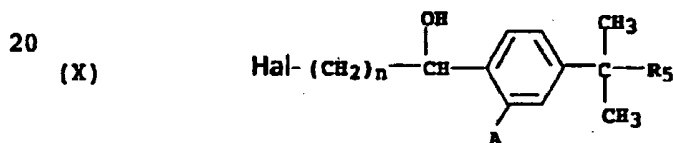


wherein

- 10 Hal is Cl, Br or I;
n is an integer of from 1 to 5; and
A is a hydrogen or hydroxy.

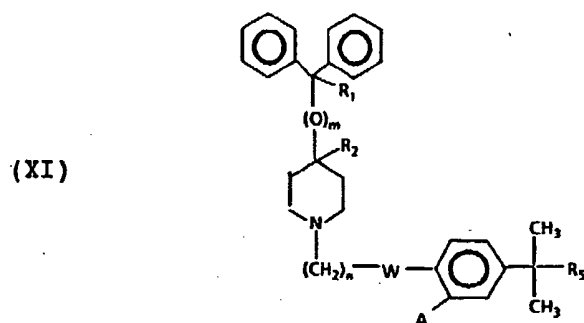


wherein A is a hydrogen or hydroxy.



wherein

- 25 Hal is Cl, Br or I;
n is an integer of from 1 to 5;
A is a hydrogen or hydroxy; and
R₅ is H, CH₂OD wherein D is hydrogen, acetate or
benzoate, CHO, Br, Cl, I, CN, -COOH, -COOalkyl or
30 -CONR₆R₇ wherein the alkyl moiety has from 1 to 6
carbon atoms and is straight or branched and R₆ and
R₇ are each independently H, C₁-C₆alkyl, C₁-C₆alkoxy
or R₆ and R₇ taken together with the nitrogen atom
form a pyrrolidine, piperidine or morpholine, with
35 the proviso that R₆ and R₇ cannot both be
represented by C₁-C₆alkoxy; and
individual optical isomers thereof.



wherein

W represents -C(=O)- or -CH(OH)-;

R₁ represents hydrogen or hydroxy;

R₂ represents hydrogen; or

R₁ and R₂ taken together form a second bond between the carbon atoms bearing R₁ and R₂;

n is an integer of from 1 to 5;

m is an integer 0 or 1;

R₅ is H, Br, Cl, I, CN or -CONR₆R₇ wherein R₆

and R₇ are each independently H, C₁-C₆alkyl, C₁-

C₆alkoxy or R₆ and R₇ taken together with the

nitrogen atom form a pyrrolidine, piperidine or

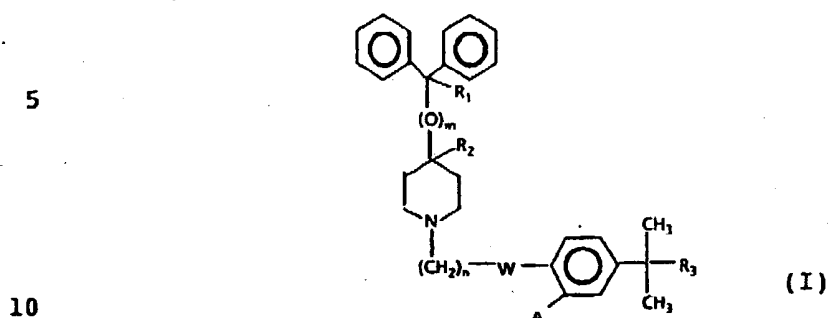
morpholine, with the proviso that R₆ and R₇ cannot both be represented by C₁-C₆alkoxy;

A is hydrogen or hydroxy; and

pharmaceutically acceptable salts and individual optical isomers thereof, with the proviso that where R₁ and R₂

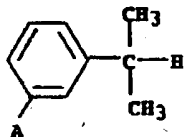
are taken together to form a second bond between the carbon atoms bearing R₁ and R₂ or where R₁ represented hydroxy, m is an integer 0.

In addition, the present invention provides novel processes for preparing the antihistaminic piperidine derivatives of formula



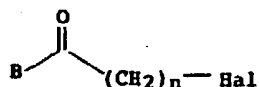
wherein

- W represents $-C(=O)-$ or $-CH(OH)-$;
- 15 R_1 represents hydrogen or hydroxy;
- R_2 represents hydrogen; or
- R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;
- n is an integer of from 1 to 5;
- 20 m is an integer 0 or 1;
- R_3 is $-COOH$ or $-COOalkyl$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;
- each of A is hydrogen or hydroxy; and
- pharmaceutically acceptable salts and individual optical
- 25 isomers thereof, with the proviso that where R_1 and R_2 are taken together to form a second bond between the carbon atoms bearing R_1 and R_2 or where R_1 represented hydroxy, m is an integer 0, comprising the steps of:
- 30 (a) reacting a cumene compound of the formula



wherein A is as defined above with a ω -halo compound of the formula

-10-



5 wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of a suitable Lewis acid to produce a ω -halo cumylketone compound;

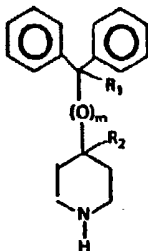
10 (b) reacting the ω -halo cumylketone compound with a suitable halogenating agent to give a ω -halo-halocumylketone compound;

15 (c) reacting the ω -halo-halocumylketone compound with a suitable cyanating agent to give a ω -halo-cyanocumylketone compound;

20 (d) reacting the ω -halo-cyanocumylketone compound with an appropriate straight or branched $\text{C}_1\text{-C}_6$ alcohol in the presence of a suitable anhydrous acid to give a ω' -halo- α' -keto- α,α -dimethylphenylacetic acid imidate compound;

25 (e) reacting the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid imidate compound with water to give a ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound;

30 (f) reacting the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound with a piperidine compound of the formula



35

wherein R_1 , R_2 and m are as defined above in the presence of a suitable non-nucleophilic base to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein
5 R_3 is COOalkyl and W is $-C(=O)-$;

(g) optionally hydrolyzing the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOalkyl and W is $-C(=O)-$ to produce a ω' -piperidine- α' -
10 hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH and W is $-C(=O)-$;

(h) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is
15 COOalkyl and W is $-C(=O)-$ or the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH and W is $-C(=O)-$ with a suitable reducing agent to produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOH$ and W is $-CH(OH)-$ or the ω' -
20 piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOalkyl$ and W is $-CH(OH)-$; and

(i) optionally reacting the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -
25 COOH and W is $-CH(OH)-$ or the appropriate ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOH$ and W is $-C(=O)-$ with an appropriate straight or branched C_1-C_6 alcohol in the presence of a suitable acid to produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl
30 derivative of formula (I) wherein R_3 is $-COOalkyl$ and W is $-CH(OH)-$ or a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative wherein R_3 is $-COOalkyl$ and W is $-C(=O)-$; and

(j) optionally reacting the ω' -piperidine- α' -keto- α,α -
35 dimethylphenyl derivative of formula (I) wherein R_3 is $-COOH$ and W is $-C(=O)-$, the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOalkyl$ and W is $-C(=O)-$, the ω' -piperidine- α' -hydroxy- α,α -

-12-

dimethylphenyl derivative of formula (I) wherein R_3 is $-\text{COOH}$
and W is $-\text{CH}(\text{OH})-$ or the ω' -piperidine- α' -hydroxy- α,α -
dimethylphenyl derivative of formula (I) wherein R_3 is -
5 COOalkyl and W is $-\text{CH}(\text{OH})-$ with an appropriate deprotecting
reagent,

with the proviso that each of the hydroxy groups present in
the compounds described in steps a-i are optionally
10 protected or unprotected.

In addition, the present invention provides novel
processes for preparing the antihistaminic piperidine
derivatives of formula

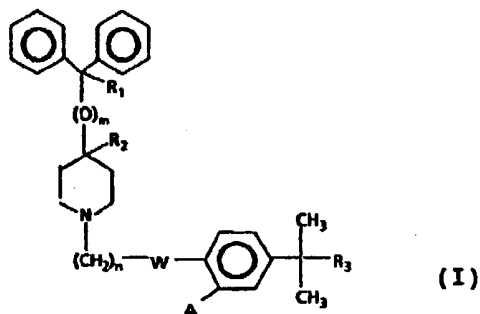
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(I)

wherein

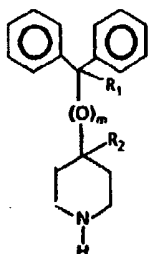
- W represents $-C(=O)-$ or $-CH(OH)-$;
R₁ represents hydrogen or hydroxy;
5 R₂ represents hydrogen; or
R₁ and R₂ taken together form a second bond between the carbon atoms bearing R₁ and R₂;
n is an integer of from 1 to 5;
m is an integer 0 or 1;
10 R₃ is $-COOH$ or $-COOalkyl$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched; each of A is hydrogen or hydroxy; and
pharmaceutically acceptable salts and individual optical isomers thereof, with the proviso that where R₁ and R₂
15 are taken together to form a second bond between the carbon atoms bearing R₁ and R₂ or where R₁ represented hydroxy, m is an integer 0, comprising the steps of:

(a) reacting a ω -halo-halocumylketone compound with
20 carbon dioxide under electrochemical reduction conditions to give a ω' -halo- α' -keto- α,α -dimethylphenylacetic compound;

(b) reacting the ω' -halo- α' -keto- α,α -dimethylphenylacetic compound with an appropriate
25 straight or branched C₁-C₆ alcohol in the presence of a suitable anhydrous acid to give a ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound;

(c) reacting the ω' -halo- α' -keto- α,α -
30 dimethylphenylacetic acid ester compound with a piperidine compound of the formula
wherein R₁, R₂ and m are as defined above in the presence of a suitable non-nucleophilic base to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein
35 R₃ is COOalkyl and W = $-C(=O)-$;

(d) optionally hydrolyzing the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R₃ is



5

10 COOalkyl and W is $-C(=O)-$ to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH and W is $-C(=O)-$;

15 (e) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOalkyl and W is $-C(=O)-$ or the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH and W is $-C(=O)-$ with a suitable reducing agent to produce a
 20 ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOH$ and W is $-CH(OH)-$ or the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOalkyl$ and W is $-CH(OH)-$; and

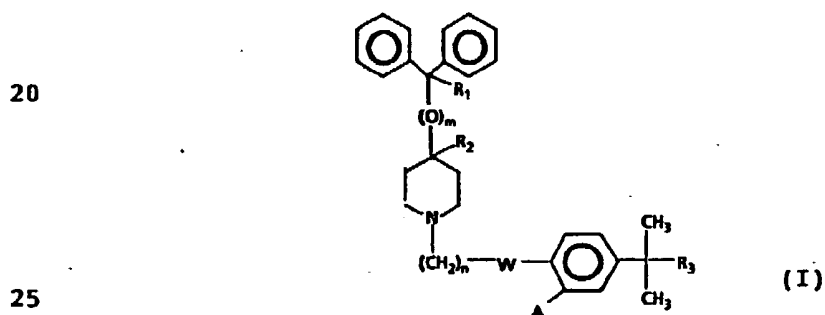
25 (f) optionally reacting the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOH$ and W is $-CH(OH)-$ or the appropriate ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOH$ and W is $-C(=O)-$ with an appropriate straight or
 30 branched C_1-C_6 alcohol in the presence of a suitable acid to produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOalkyl$ and W is $-CH(OH)-$ or a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOalkyl$ and W is $-C(=O)-$; and
 35

(g) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOH$ and W is $-C(=O)-$, the ω' -piperidine- α' -keto- α,α -

dimethylphenyl derivative of formula (I) wherein R_3 is -COOalkyl and W is -C(=O)-, the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOH and W is -CH(OH)- or the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOalkyl and W is -CH(OH)- with an appropriate deprotecting reagent,

10 with the proviso that each of the hydroxy groups present in the compounds described in steps a-f are optionally protected or unprotected.

In addition, the present invention provides novel
15 processes for preparing the antihistaminic piperidine derivatives of formula



30

35

wherein

W represents $-C(=O)-$ or $-CH(OH)-$;

R_1 represents hydrogen or hydroxy;

5 R_2 represents hydrogen; or

R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;

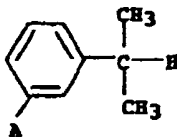
n is an integer 3;

m is an integer 0 or 1;

10 R_3 is $-COOH$ or $-COOalkyl$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched; each of A is hydrogen or hydroxy; and pharmaceutically acceptable salts and individual optical isomers thereof, with the proviso that where R_1 and R_2 are taken together to form a second bond between the carbon atoms bearing R_1 and R_2 or where R_1 represented hydroxy, m is an integer 0, comprising the steps of:

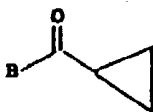
(a) reacting a cumyl compound of the formula

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25 wherein A is as defined above with an appropriate cyclopropyl compound of the structure

30



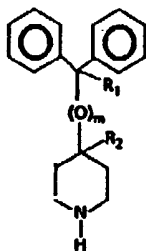
wherein B is halo or hydroxy, in the presence of a suitable Lewis acid to produce a cyclopropyl cumylketone compound;

35 (b) reacting the cyclopropyl cumylketone compound with a suitable halogenating agent to give a cyclopropyl halocumylketone compound;

(c) reacting the cyclopropyl halocumylketone compound with carbon dioxide under electrochemical reduction conditions to give a cyclopropylketo- α,α -dimethylphenylacetic acid compound;

(d) reacting the cyclopropylketo- α,α -dimethylphenylacetic with an appropriate straight or branched C_1 - C_6 alcohol in the presence of a suitable anhydrous acid to give a ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound;

(e) reacting the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound with a piperidine compound of the formula



wherein R_1 , R_2 and m are as defined above in the presence of a suitable non-nucleophilic base to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOalkyl and $W = -C(=O)-$;

(f) optionally hydrolyzing the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOalkyl and W is $-C(=O)-$ to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH and W is $-C(=O)-$;

(g) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOalkyl and W is $-C(=O)-$ or the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH

and W is -C(=O)- with a suitable reducing agent to produce a
ω'-piperidine-α'-hydroxy-α,α-dimethylphenyl derivative of
formula (I) wherein R₃ is -COOH and W is -CH(OH)- or the ω'-
5 piperidine-α'-hydroxy-α,α-dimethylphenyl derivative of
formula (I) wherein R₃ is -COOalkyl and W is -CH(OH)-; and

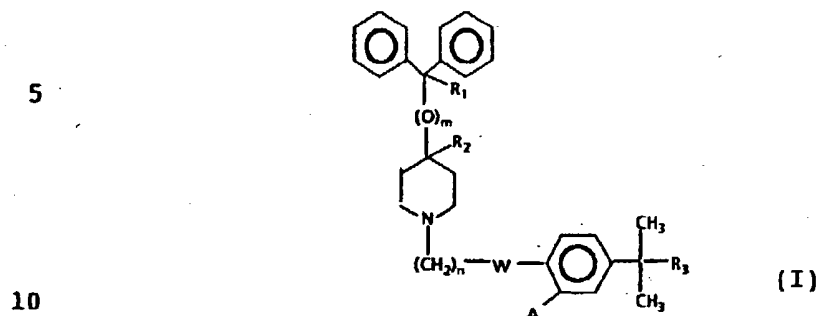
(h) optionally reacting the ω'-piperidine-α'-hydroxy-
α,α-dimethylphenyl derivative of formula (I) wherein R₃ is -
10 COOH and W is -CH(OH)- or the appropriate ω'-piperidine-α'-
keto-α,α-dimethylphenyl derivative of formula (I) wherein R₃
is -COOH and W is -C(=O)- with an appropriate straight or
branched C₁-C₆ alcohol in the presence of a suitable acid to
produce a ω'-piperidine-α'-hydroxy-α,α-dimethylphenyl
15 derivative of formula (I) wherein R₃ is -COOalkyl and W is
-CH(OH)- or a ω'-piperidine-α'-keto-α,α-dimethylphenyl
derivative of formula (I) wherein R₃ is -COOalkyl and W is -
C(=O)-; and

20 (i) optionally reacting the ω'-piperidine-α'-keto-α,α-
dimethylphenyl derivative of formula (I) wherein R₃ is -COOH
and W is -C(=O)-, the ω'-piperidine-α'-keto-α,α-
dimethylphenyl derivative of formula (I) wherein R₃ is -
COOalkyl and W is -C(=O)-, the ω'-piperidine-α'-hydroxy-α,α-
25 dimethylphenyl derivative of formula (I) wherein R₃ is -COOH
and W is -CH(OH)- or the ω'-piperidine-α'-hydroxy-α,α-
dimethylphenyl derivative of formula (I) wherein R₃ is -
COOalkyl and W is -CH(OH)- with an appropriate deprotecting
reagent,

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with the proviso that each of the hydroxy groups present in
the compounds described in steps a-h are optionally
protected or unprotected.

35 Another embodiment of the present invention involves a
process for preparing the piperidine derivatives of formula



wherein

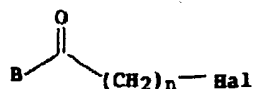
- W represents $-C(=O)-$ or $-CH(OH)-$;
- 15 R_1 represents hydrogen or hydroxy;
- R_2 represents hydrogen; or
- R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;
- n is an integer of from 1 to 5;
- 20 m is an integer 0 or 1;
- R_3 is $-COOH$ or $-COOalkyl$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;
- each of A is hydrogen or hydroxy; and
- pharmaceutically acceptable salts and individual optical
- 25 isomers thereof, with the proviso that where R_1 and R_2 are taken together to form a second bond between the carbon atoms bearing R_1 and R_2 or where R_1 represented hydroxy, m is an integer 0, comprising the steps of:

- 30 (a) reacting a α,α -dimethylphenylacetic acid amide compound of the formula



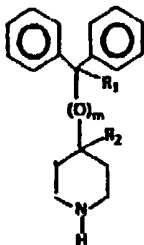
wherein A is as defined above and R_6 and R_7 are each independently H, C_1-C_6alkyl , $C_1-C_6alkoxy$ or R_6 and R_7 taken

together with the nitrogen atom for a pyrrolidine, piperidine or morpholine, with the proviso that R_6 and R_7 cannot both be represented by C_1-C_6 alkoxy with a ω -halo compound of the formula



wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of a suitable Lewis acid to produce a ω' -halo- α' -keto- α,α -dimethylphenylacetic acid amide compound;

(b) reacting the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid amide compound with a piperidine compound of the formula



wherein R_1 and R_2 are as defined above in the presence of a suitable non-nucleophilic base to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (XI) wherein R_5 is $-\text{CONR}_6\text{R}_7$ wherein R_6 and R_7 are as defined above;

(c) optionally hydrolyzing the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (XI) wherein R_5 is $-\text{CONR}_6\text{R}_7$ wherein R_6 and R_7 are as defined above to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH and W is $-\text{C}(=\text{O})-$;

(d) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH and W is $-C(=O)-$ with a suitable reducing agent to produce a
5 ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOH$ and W is $-CH(OH)-$; and

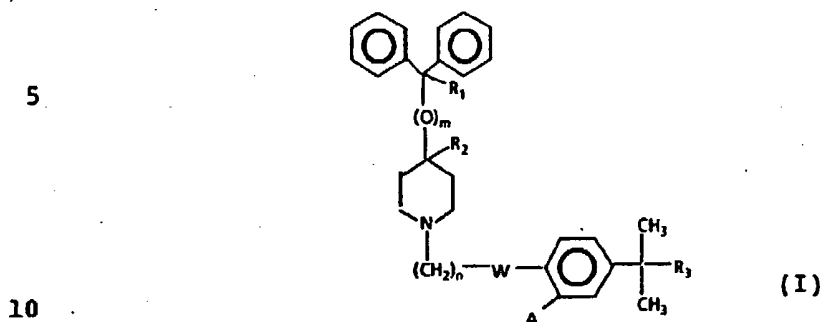
(e) optionally reacting the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -
10 COOH and W is $-CH(OH)-$ or the appropriate ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOH$ and W is $-C(=O)-$ with an appropriate straight or branched C_1-C_6 alcohol in the presence of a suitable acid to produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl
15 derivative of formula (I) wherein R_3 is $-COOalkyl$ and W is $-CH(OH)-$ or a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOalkyl$ and W is $-C(=O)-$; and

(f) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOH$ and W is $-C(=O)-$, the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOalkyl$ and W is $-C(=O)-$, the ω' -piperidine- α' -hydroxy- α,α -
25 dimethylphenyl derivative of formula (I) wherein R_3 is $-COOH$ and W is $-CH(OH)-$ or the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOalkyl$ and W is $-CH(OH)-$ with an appropriate deprotecting reagent,

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with the proviso that each of the hydroxy groups present in the compounds described in steps a-e are optionally protected or unprotected.

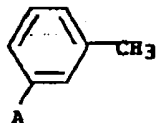
35 Another embodiment of the present invention involves a process for preparing the piperidine derivatives of formula



wherein

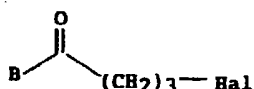
- W represents $-C(=O)-$ or $-CH(OH)-$;
- 15 R_1 represents hydrogen or hydroxy;
- R_2 represents hydrogen; or
- R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;
- n is an integer of from 1 to 5;
- 20 m is an integer 0 or 1;
- R_3 is $-COOH$ or $-COOalkyl$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;
- each of A is hydrogen or hydroxy; and
- pharmaceutically acceptable salts and individual optical
- 25 isomers thereof, with the proviso that where R_1 and R_2 are taken together to form a second bond between the carbon atoms bearing R_1 and R_2 or where R_1 represented hydroxy, m is an integer 0, comprising the steps of:

- 30 (a) reacting a toluene compound of the formula

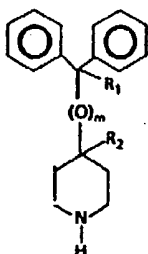


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wherein A is as defined above with a ω -halo compound of the formula



- 5 wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of a suitable Lewis acid to produce a ω -halo-tolylketone compound;
- 10 (b) reacting the ω -halo-tolylketone compound with a suitable base to give a cyclopropyl-tolylketone compound;
- (c) reacting the cyclopropyl-tolylketone compound with a suitable halogenating agent to give a cyclopropyl-halotolylketone compound;
- 15 (d) reacting the cyclopropyl-halotolylketone compound with a suitable cyanating agent to give a cyclopropyl cyanotolylketone compound;
- 20 (e) reacting the cyclopropyl cyanotolylketone compound with a suitable methylating agent to give a cyclopropyl cyanocumylketone compound;
- 25 (f) reacting the cyclopropyl cyanocumylketone compound with a suitable base to give a cyclopropylketo- α,α -dimethylphenylacetic acid amide;
- (g) reacting the cyclopropylketo- α,α -dimethylphenylacetic acid amide with an appropriate straight or branched C₁-C₆ alcohol in the presence of a suitable anhydrous acid to give a ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound;
- 30 (h) reacting the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound with a piperidine compound of the formula
- 35



5

10 wherein R_1 , R_2 and m are as defined above in the presence of a suitable non-nucleophilic base to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative;

15 (i) optionally hydrolyzing the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH and W is $-\text{C}(=\text{O})-$;

20 (j) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH and W is $-\text{C}(=\text{O})-$ with a suitable reducing agent to produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-\text{COOH}$ and W is $-\text{CH}(\text{OH})-$; and

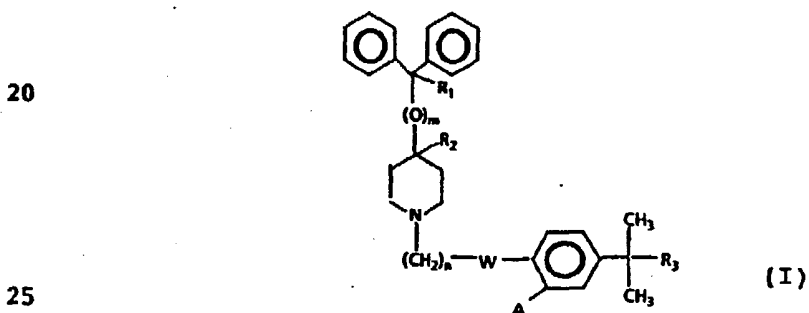
25 (k) optionally reacting the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-\text{COOH}$ and W is $-\text{CH}(\text{OH})-$ or the appropriate ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-\text{COOH}$ and W is $-\text{C}(=\text{O})-$ with an appropriate straight or
30 branched C_1 - C_6 alcohol in the presence of a suitable acid to produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-\text{COOalkyl}$ and W is $-\text{CH}(\text{OH})-$ or a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (II) wherein R_3 is $-\text{COOalkyl}$ and W is
35 $-\text{C}(=\text{O})-$; and

(l) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (II) wherein R_3 is -

COOH and W is $-C(=O)-$, the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (II) wherein R_3 is $-COOalkyl$ and W is $-C(=O)-$, the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOH$ and W is $-CH(OH)-$ or the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl of formula (I) wherein R_3 is $-COOalkyl$ and W is $-CH(OH)-$ with an appropriate deprotecting reagent,

10 with the proviso that each of the hydroxy groups present in the compounds described in steps a-k are optionally protected or unprotected.

Another embodiment of the present invention involves a
15 process for preparing the piperidine derivatives of formula



wherein

W represents $-C(=O)-$ or $-CH(OH)-$;

R_1 represents hydrogen or hydroxy;

5 R_2 represents hydrogen; or

R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;

n is an integer of from 1 to 5;

m is an integer 0 or 1;

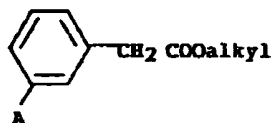
10 R_3 is $-COOH$ or $-COOalkyl$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;

each of A is hydrogen or hydroxy; and

pharmaceutically acceptable salts and individual optical isomers thereof, with the proviso that where R_1 and R_2

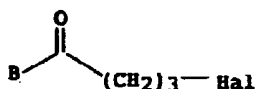
15 are taken together to form a second bond between the carbon atoms bearing R_1 and R_2 or where R_1 represented hydroxy, m is an integer 0, comprising the steps of:

(a) reacting a phenylacetic acid ester compound of the
20 formula



25

wherein A is as defined above with a ω -halo compound of the formula



30

wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of a suitable Lewis acid to produce a ω' -halo- α' -keto-phenylacetic acid ester
35 compound;

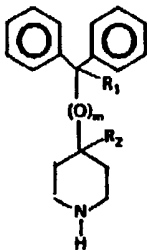
(b) reacting the ω' -halo- α' -keto-phenylacetic acid ester compound with a suitable methylating agent in the

presence of a suitable base to give a cyclopropylketo- α,α -dimethylphenylacetic acid ester;

5 (c) purifying the cyclopropylketo- α,α -dimethylphenylacetic acid ester by distillation and/or recrystallization;

(d) reacting the cyclopropylketo- α,α -
10 dimethylphenylacetic acid ester with an appropriate straight or branched C_1 - C_6 alcohol in the presence of a suitable anhydrous acid to give a ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound;

15 (e) reacting the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound with a piperidine compound of the formula



wherein R_1 , R_2 and m are as defined above in the presence of a suitable non-nucleophilic base to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOalkyl and W is -C(=O)-;

30

(f) optionally hydrolyzing the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOalkyl and W is -C(=O)- to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH and W is -C(=O)-;

35

(g) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH,

and W is -C(=O)- with a suitable reducing agent to produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOH and W is -CH(OH)-; and

5

(h) optionally reacting the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOH and W is -CH(OH)- or the appropriate ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOH and W is -C(=O)- with an appropriate straight or branched C_1 - C_6 alcohol in the presence of a suitable acid to produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOalkyl and W is -CH(OH)- or a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOalkyl and W is -C(=O)-; and

(i) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOH and W is -C(=O)-, the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOalkyl and W is -C(=O)-, the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOH and W is -CH(OH)- or the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl of formula (I) wherein R_3 is -COOalkyl and W is -CH(OH)- with an appropriate deprotecting reagent,

with the proviso that each of the hydroxy groups present in the compounds described in steps a-h are optionally protected or unprotected.

(g) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH and W is -C(=O)- with a suitable reducing agent to produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOH and W is -CH(OH)-; and

- (h) optionally reacting the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -
5 COOH and W is -CH(OH)- or the appropriate ω' -piperidine- α' -
keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3
is -COOH and W is -C(=O)- with an appropriate straight or
branched C_1 - C_6 alcohol in the presence of a suitable acid to
produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl
10 derivative of formula (I) wherein R_3 is -COOalkyl and W is -
CH(OH)- or a ω' -piperidine- α' -keto- α,α -dimethylphenyl
derivative of formula (I) wherein R_3 is -COOalkyl and W is -
C(=O)-; and
- 15 (i) optionally reacting the ω' -piperidine- α' -keto- α,α -
dimethylphenyl derivative of formula (I) wherein R_3 is -COOH
and W is -C(=O)-, the ω' -piperidine- α' -keto- α,α -
dimethylphenyl derivative of formula (I) wherein R_3 is -
COOalkyl and W is -C(=O)-, the ω' -piperidine- α' -hydroxy- α,α -
20 dimethylphenyl derivative of formula (I) wherein R_3 is -COOH
and W is -CH(OH)- or the ω' -piperidine- α' -hydroxy- α,α -
dimethylphenyl of formula (I) wherein R_3 is -COOalkyl and W
is -CH(OH)- with an appropriate deprotecting reagent,
- 25 with the proviso that each of the hydroxy groups present in
the compounds described in steps a-h are optionally
protected or unprotected.

As used herein, the term " C_1 - C_6 alkyl" or "alkyl" refers
30 to a straight or branched alkyl group having from 1 to 6
carbon atoms and as referred to herein are methyl, ethyl, n-
propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl,
neopentyl and n-hexyl. The term " C_1 - C_6 alkoxy" refers to a
straight or branched alkoxy group having from 1 to 6 carbon
35 atoms and as referred to herein are methoxy, ethoxy, n-
propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, n-
pentoxy, neopentoxy and n-hexoxy. The term "Hal" or "halo"
refers to a halogen group and includes Cl, Br or I.

The piperidine derivatives of the formula (IX) can form pharmaceutically acceptable salts. Pharmaceutically acceptable acid addition salts of the compounds of this invention are those of any suitable inorganic or organic acid. Suitable inorganic acids are, for example, hydrochloric, hydrobromic, sulfuric, and phosphoric acids. Suitable organic acids include carboxylic acids, such as, acetic, propionic, glycolic, lactic, pyruvic, malonic, succinic, fumaric, malic, tartaric, citric, cyclamic, ascorbic, maleic, hydroxymaleic, and dihydroxymaleic, benzoic, phenylacetic, 4-aminobenzoic, 4-hydroxybenzoic, anthranillic, cinnamic, salicylic, 4-aminosalicylic, 2-phenoxybenzoic, 2-acetoxybenzoic, and mandelic acid, sulfonic acids, such as, methanesulfonic, ethanesulfonic and β -hydroxyethanesulfonic acid. Non-toxic salts of the compounds of the above-identified formula formed with inorganic or organic bases are also included within the scope of this invention and include, for example, those of alkali metals, such as, sodium, potassium and lithium, alkaline earth metals, for example, calcium and magnesium, light metals of group IIIA, for example, aluminum, organic amines, such as, primary, secondary or tertiary amines, for example, cyclohexylamine, ethylamine, pyridine, methylaminoethanol and piperazine. The salts are prepared by conventional means as, for example, by treating a piperidine derivative of formula (I) with an appropriate acid or base.

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35

The novel intermediates of formula (II), formula (III), formula (IV), formula (V), formula (VI) and formula (VII) wherein R_5 is hydrogen may be prepared as described in 5 Scheme A. In Scheme A, all substituents are as previously defined unless otherwise indicated.

Scheme A

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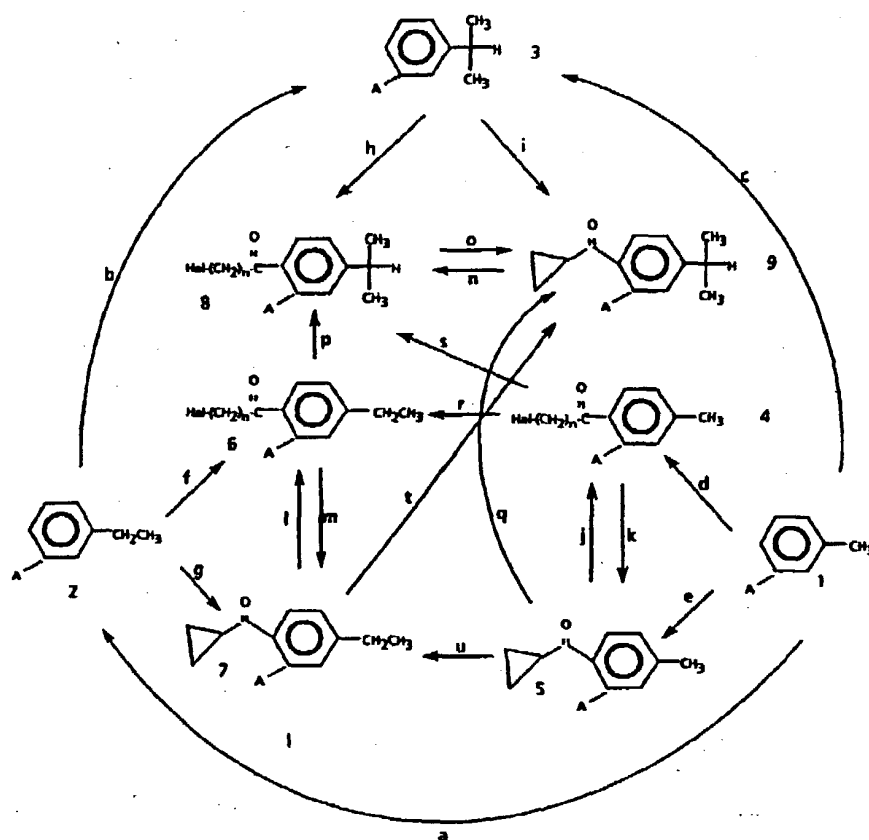
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Scheme A provides various general synthetic procedures for preparing the novel intermediates of formula (II), formula (III) and formula (IV) wherein R_5 is hydrogen.

In step a, the appropriate toluene derivative of structure (1) is methylated to give the corresponding ethylbenzene derivative of structure (2).

For example, the appropriate toluene derivative of structure (1) is reacted with a slight molar excess of an appropriate methylating agent, such as iodomethane, chloromethane or bromomethane in the presence of a suitable non-nucleophilic base, such as potassium t-butoxide or sodium hydride. The reaction is typically conducted in a suitable organic solvent, such as diglyme, tert-butyl methyl ether or methylene chloride, for a period of time ranging from 30 minutes to 24 hours and at a temperature range of from -78°C to room temperature. The corresponding ethylbenzene derivative of structure (2) is recovered from the reaction zone by extractive methods as is known in the art and may be purified by distillation.

20

In step b, the appropriate ethylbenzene derivative of structure (2) is methylated to give the corresponding cumene derivative of structure (3) as described previously in step a, but using at least 2 molar equivalents of methylating agent.

In step c, the appropriate toluene derivative of structure (1) is dimethylated to give the corresponding cumene derivative of structure (3) as described previously in step a but using at least 2 molar equivalents of methylating agent.

In step d, the appropriate toluene derivative of structure (1) is acylated with an appropriate ω -halo compound of the structure $\text{Hal}-(\text{CH}_2)_n-\text{C}(=\text{O})-\text{B}$, wherein B is Hal or hydroxy, Hal is Cl, Br or I and n is as previously defined to give the corresponding ω -halo tolylketone compound of structure (4).

For example, the appropriate ω -halo tolylketone compound of structure (4) may be prepared by reacting an appropriate toluene derivative of structure (1) with an appropriate ω -halo compound of the structure $\text{Hal}-(\text{CH}_2)_n-\text{C}(=\text{O})-\text{B}$, wherein B is Hal or hydroxy, Hal is Cl, Br or I and n is as previously defined, which are known in the art or are prepared by procedures well known in the art, under the general conditions of a Friedel-Crafts acylation using a suitable Lewis acid. The reaction is carried out in a solvent, such as carbon disulfide, 1,2-dichloroethane, n-hexane, acetonitrile, 1-nitropropane, nitromethane, diethyl ether and carbon tetrachloride, methylene chloride, tetrachloroethane or nitrobenzene with methylene chloride being the preferred solvent. The reaction time varies from about 1/2 hour to 25 hours, preferably 10 to 16 hours and the reaction temperature varies from about 0°C to 25°C. The corresponding ω -halo tolylketone compound of structure (4) is recovered from the reaction zone by an aqueous quench followed by extraction as is known in the art. The ω -halo tolylketone compound of structure (4) may be purified by procedures well known in the art, such as crystallization and/or distillation.

25

Alternatively, the appropriate toluene derivative of structure (1) may be acylated with the ω -halo compound of the structure $\text{Hal}-(\text{CH}_2)_n-\text{C}(=\text{O})-\text{B}$, wherein B is hydroxy, Hal is Cl, Br or I and n is as previously defined in the presence of a Lewis acid to give the corresponding ω -halo tolylketone compound of structure (4) as described in *Arch. Pharm.* 306, 807 1973. In general, an appropriate toluene derivative of structure (1) and the ω -halo compound of the structure $\text{Hal}-(\text{CH}_2)_n-\text{C}(=\text{O})-\text{B}$, wherein B is hydroxy, are melted together at about 50°C, then cooled to about 10°C after which a Lewis acid is added in an amount about 2.2 times the molar amount of the appropriate toluene derivative of structure (1) employed. The mixture is

30

heated at about 70°C for about 2 hours after which a 30% sodium acetate solution is added and extracted with ether. The organic layer is dried and the solvent evaporated to
5 give the corresponding ω -halo tolylketone compound of structure (4). The ω -halo tolylketone compound of structure (4) may be purified by procedures well known in the art, such as crystallization and/or distillation.

10 Suitable Lewis acids for the acylation reaction described in step d are well known and appreciated in the art. Examples of suitable Lewis acids are boron trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride, ferric chloride,
15 cobalt(II) chloride and zinc chloride, with aluminum chloride being preferred. The selection and utilization of suitable Lewis acids for the acylation reaction of step d is well known and appreciated by one of ordinary skill in the art.

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The starting ω -halo compound of the structure Hal- $(CH_2)_n-C(=O)-B$, wherein B is Hal or hydroxy, Hal is Cl, Br or I and n is as previously defined are commercially available or easily prepared by generally known methods.

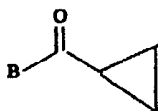
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While also not necessary for utilization in the acylation reaction of step d, the phenol functionality of those toluene derivatives of structure (1), wherein A is hydroxy may be protected with a suitable protecting group.
30 For example, suitable protecting groups for the phenolic hydroxy include methyl ether, 2-methoxyethoxymethyl ether (MEM), cyclohexyl ether, o-nitrobenzyl ether, 9-anthryl ether, t-butyldimethylsilyl ether, acetate, benzoate, methyl carbamate, benzyl carbamate, aryl pivaloate and aryl
35 methanesulfonate.

In step e, to appropriate toluene derivative of

structure (1) is acylated with an appropriate cyclopropyl compound of the structure

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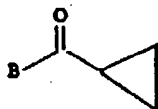
wherein B is as previously defined to give the
10 corresponding cyclopropyl tolylketone derivative of
structure (5) as described previously in step d.

In step f, the appropriate ethylbenzene derivative of
structure (2) is acylated with an appropriate ω -halo
15 compound of the structure $\text{Hal}-(\text{CH}_2)_n-\text{C}(=\text{O})-\text{B}$, wherein B is
Hal or hydroxy, Hal is Cl, Br or I and n is as previously
defined to give the corresponding ω -halo ethylphenylketone
compound of structure (6) as described previously in step
d.

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In step g, the appropriate ethylbenzene derivative of
structure (2) is acylated with an appropriate cyclopropyl
compound of the structure

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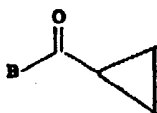
wherein B is as previously defined to give the corresponding cyclopropyl ethylphenylketone derivative of structure (7) as described previously in step e.

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In step h, the appropriate cumene derivative of structure (3) is acylated with an appropriate ω -halo compound of the structure $\text{Hal}-(\text{CH}_2)_n-\text{C}(=\text{O})-\text{B}$, wherein B is Hal or hydroxy, Hal is Cl, Br or I and n is as previously defined to give the corresponding ω -halo cumylketone compound of structure (8) as described previously in step d.

In step i, to appropriate cumene derivative of structure (3) is acylated with an appropriate cyclopropyl compound of the structure

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wherein B is as previously defined to give the corresponding cyclopropyl cumylketone derivative of structure (9) as described previously in step e.

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In step j, the cyclopropyl functionality of the appropriate cyclopropyl tolylketone derivative of structure (5) is ring-opened to give the corresponding ω -halo tolylketone compound of structure (4) wherein $n = 3$.

30

For example, the appropriate cyclopropyl tolylketone derivative of structure (5) is reacted with an appropriate hydrogen halide in a suitable organic solvent, such as toluene, xylene and ethanol. The reaction is typically conducted at a temperature range of from room temperature to 70°C and for a period of time ranging from 20 minutes to 10 hours. The corresponding ω -halo tolylketone compound of structure (4) wherein $n = 3$ is isolated from the reaction

35

zone by evaporation of the solvent or may be stored in a solution of the hydrogen halide.

5 In step k, the appropriate ω -halo tolylketone compound of structure (4) wherein $n = 3$ is ring-closed to give the corresponding cyclopropyl tolylketone derivative of structure (5).

10 For example, the appropriate ω -halo tolylketone compound of structure (4) wherein $n = 3$ is reacted with an appropriate non-nucleophilic base, such as sodium hydroxide or potassium hydroxide in a suitable organic protic solvent, such as methanol or ethanol. The reaction is
15 typically conducted at a temperature range of from -10°C to room temperature and for a period of time ranging from 10 minutes to 5 hours. The corresponding cyclopropyl tolylketone derivative of structure (5) is isolated from the reaction zone by extractive methods as are known in the
20 art and may be purified by distillation.

In step l, the cyclopropyl functionality of the appropriate cyclopropyl ethylphenylketone derivative of structure (7) is ring-opened to give the corresponding ω -
25 halo ethylphenylketone compound of structure (6) wherein $n = 3$ as described previously in step j.

In step m, the appropriate ω -halo ethylphenylketone compound of structure (6) wherein $n = 3$ is ring-closed to
30 give the corresponding cyclopropyl ethylphenylketone derivative of structure (7) as described previously in step k.

In step n, the cyclopropyl functionality of the
35 appropriate cyclopropyl cumylketone derivative of structure (9) is ring-opened to give the corresponding ω -halo cumylketone compound of structure (8) wherein $n = 3$ as described previously in step j.

In step o, the appropriate ω -halo cumylketone compound of structure (8) wherein $n = 3$ is ring-closed to give the
5 corresponding cyclopropyl cumylketone derivative of structure (9) as described previously in step k.

In step p, the appropriate ω -halo ethylphenylketone compound of structure (6) is methylated to give the
10 corresponding ω -halo cumylketone compound of structure (8) as described previously in step a.

In step q, the appropriate cyclopropyl tolylketone derivative of structure (5) is dimethylated to give the
15 corresponding cyclopropyl cumylketone derivative of structure (9) as described previously in step c.

In step r, the appropriate ω -halo tolylketone compound of structure (4) is methylated to give the corresponding ω -
20 halo ethylphenylketone compound of structure (6) as described previously in step a.

In step s, the appropriate ω -halo tolylketone compound of structure (4) is dimethylated to give the corresponding
25 ω -halo cumylketone compound of structure (8) as described previously in step c.

In step t, the appropriate cyclopropyl ethylphenylketone derivative of structure (7) is methylated
30 to give the corresponding cyclopropyl cumylketone derivative of structure (9) as described previously in step a.

In step u, the appropriate cyclopropyl tolylketone derivative of structure (5) is methylated to give the
35 corresponding cyclopropyl ethylphenylketone derivative of structure (7) as described previously in step a.

Starting materials for use in Scheme A are readily available to one of ordinary skill in the art.

- 5 The following examples present typical syntheses as described in Scheme A. These examples are understood to be illustrative only and are not intended to limit the scope of the present invention in any way. As used herein, the following terms have the indicated meanings: "g" refers to
- 10 grams; "mmol" refers to millimoles; "mL" refers to milliliters; "bp" refers to boiling point; "°C" refers to degrees Celsius; "mm Hg" refers to millimeters of mercury; "μL" refers to microliters; "μg" refers to micrograms; and "μM" refers to micromolar.

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Example 1

Step h: 4-Chloro-1-(4-isopropyl-phenyl)-butan-1-one

- Slurry aluminum chloride (140.9g, 1.075mol) and 4-chlorobutyl chloride (148g, 1.05mol) in methylene
- 20 chloride (1.0L) add, by dropwise addition, cumene (125g, 1.04mol) over a thirty minute period under a nitrogen atmosphere while maintaining the internal temperature between 5-8°C with an ice bath. Allow the stirred solution to come to room temperature and continue stirring under
- 25 nitrogen for 14 hours. Cautiously add the methylene chloride solution to 1L of crushed ice with stirring and add additional methylene chloride (400mL). Separate the organic phase and wash with 10% hydrochloric acid (3X300mL), water (3X300mL), 10% sodium bicarbonate
- 30 (3X300mL) and water (3X300mL). Dry (MgSO₄), filter and wash with methylene chloride (150mL). Evaporate the solvent to give the title compound (203g, 86%) as a clear oil which crystallizes on standing; mp 35-37°C.
- 35 ¹H NMR (300MHz, CDCl₃) δ 7.91 (d, J=8.2Hz, 2H), 7.31 (d, J=8.2Hz, 2H), 3.65 (t, J=6.3Hz, 2H), 3.13 (t, J=6.9Hz, 2H), 2.95 (p, J=6.9Hz, 1H), 2.20 (p, J=6.6Hz, 2H), 1.26 (d, J=6.9Hz, 6H); ¹³C NMR (75MHz, CDCl₃) δ 198.2, 154.4, 134.4,

128.1, 126.5, 44.5, 32.96, 34.0, 26.7, 23.5; IR (CDCl₃)
2950, 2920, 1675, 1680, 1600, 1410, 1225 cm⁻¹; MS (GCCIMS
(methane)) 255 (3), 251 (10), 227 (30 (M+H)), 225 (100
5 (M+H)), 189 (70), 147 (95), 107 (13, 105 (40).

Anal. Calcd for C₁₃H₁₇OCl: C, 69.48; H, 7.62; Found: C,
69.31; H, 7.39.

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Example 2Step d: 4-Chloro-1-(4-methyl-phenyl)-butan-1-one

Suspend anhydrous AlCl₃ (156g, 1.15mol) in toluene (1500mL)
and cool to 2-4°C. Add, by slow addition, a solution of 4-
chlorobutyryl chloride (165.5g, 1.15mol) in toluene
15 (300mL). Stir for 15 minutes and pour into stirring ice-
water (2.5L). Stir for 30 hours, decant the toluene and
extract the aqueous phase with toluene (700mL). Combine
the organic layers and wash three times with water (1L, 1L,
500mL). Evaporate the solvent in vacuo to give the title
20 compound as a pale yellow oil (292.3g, 95%).

Example 3Step k: Cyclopropyl-p-tolyl-methanone

Dissolve potassium hydroxide (126g) in methanol (450mL),
25 stir and cool in an ice-water bath. Add, by dropwise
addition, a solution of 4-chloro-1-(4-methyl-phenyl)-butan-
1-one (292g) in methanol (450mL). Stir for 20 minutes at
8-10°C and partially evaporate the methanol in vacuo to
give 400mL of a residue. Pour the residue, with stirring,
30 into water (1500mL), filter the white solid and dry under
vacuum to give the title compound as a white solid (190.8g,
90%).

The following compounds can be prepared using the
35 methodology depicted in Scheme A:

Cyclopropyl-(4-isopropyl-phenyl)-methanone;

Cyclopropyl-(4-ethyl-phenyl)-methanone; and

4-Chloro-1-(4-ethyl-phenyl)-butan-1-one.

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The novel intermediates of formula (II), formula (III), formula (IV), formula (V), formula (VI) and formula (VII) wherein R₅ is OH, Cl, Br or I may be prepared as described in Scheme B. In Scheme B, all substituents are as previously defined unless otherwise indicated.

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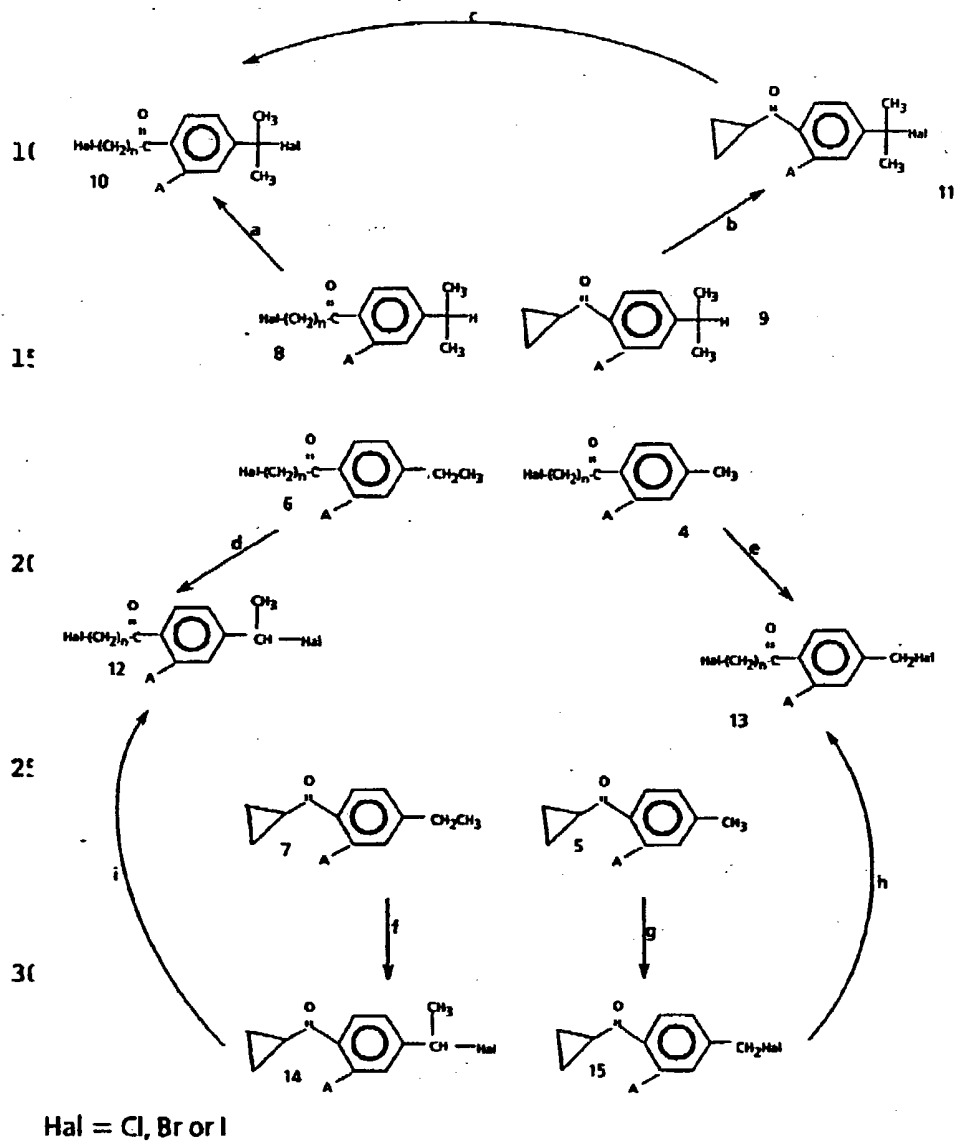
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Scheme B



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Scheme B provides various general synthetic procedures for preparing the novel intermediates of formula (II),

formula (III), formula (IV), formula (V), formula (VI) and formula (VII) wherein R₅ is OH, Cl, Br or I.

- 5 In step a, the appropriate ω -halo cumylketone compound of structure (8) is halogenated to give the corresponding ω -halo-halocumylketone compound of structure (10).

For example, the appropriate ω -halo-halocumylketone
10 compound of structure (10) may be prepared by reacting an appropriate ω -halo cumylketone compound of structure (8) with a suitable halogenating agent optionally in the presence of a catalytic amount of a suitable initiator. Examples of suitable brominating agents are N-
15 bromosuccinimide, and 1,3-dibromo-5,5-dimethyl hydantoin, with N-bromosuccinimide being preferred. An example of suitable chlorinating agent is N-chlorosuccinimide and an example of a suitable iodinating agent is N-iodosuccinimide. Examples of suitable initiators are benzoyl peroxide, AIBN,
20 t-butyl peroxide and ultraviolet light. The reaction is carried out in a solvent, such as carbon tetrachloride, methylene chloride, 1,2-dichlorobenzene, 1,2-dichloroethane, ethyl formate or ethyl acetate, with carbon tetrachloride being the preferred solvent. The reaction
25 time varies from about 1/2 hour to 8 hours, preferably 1/2 to 2 hours and the reaction temperature varies from about 25°C to the reflux temperature of the solvent employed, preferably 70°C to 80°C. The corresponding ω -halo-halocumylketone compound of structure (10) is recovered
30 from the reaction zone by extractive methods as are known in the art followed by evaporation of the solvent.

In addition, the halogenation reaction of step a may be carried out in a 2-phase procedure. For example, the
35 appropriate ω -halo-halocumylketone compound of structure (10) may be prepared by reacting an appropriate ω -halo cumylketone compound of structure (8) with a suitable halogenating agent, such as sodium bromate/sodium bromide,

in a solvent mixture such as methylene chloride and water, catalyzing the reaction with, for example, ultraviolet light. The corresponding ω -halo-halocumylketone compound of structure (10) is recovered from the reaction zone by extractive methods as are known in the art followed by evaporation of the solvent.

The ω -halo-halocumylketone compound of structure (10) may dehydrohalogenate to the corresponding α -methylstyrene, giving various mixtures of ω -halo-halocumylketone compound of structure (10) and α -methylstyrene compounds. The α -methylstyrene compounds in such a mixture may be back-converted to ω -halo-halocumylketone compound of structure (10) by treatment with anhydrous hydrogen halide gas. Typically, a solution of the mixture of ω -halo-halocumylketone compound of structure (10) and α -methylstyrene compounds in a suitable organic solvent, such as methylene chloride or acetonitrile, is treated with a suitable anhydrous hydrogen halide gas, such as hydrogen chloride. The reaction is typically treated with the hydrogen halide gas for a period of time ranging from 30 minutes to 5 hours and at a temperature range of from 0°C to room temperature. The remediated ω -halo-halocumylketone compound of structure (10) may be isolated by evaporation of solvent, but may be stored as a solution in the organic solvent containing hydrogen halide gas.

In addition, halogen exchange of the benzylic halogen can be accomplished by thorough solvolysis in the presence of the appropriate hydrogen halide.

For example, the ω -chloro-halocumylketone compound of structure (10) can be prepared from the ω -bromo-halocumylketone compound of structure (10) by thorough aqueous solvolysis in the presence of hydrogen chloride.

In step b, the appropriate cyclopropyl cumylketone derivative of structure (9) is halogenated to give the corresponding cyclopropyl halocumylketone compound of structure (11) as described previously in step a.

In step c, the cyclopropyl functionality of the appropriate cyclopropyl halocumylketone compound of structure (11) is ring-opened to give the corresponding ω -halo-halocumylketone compound of structure (10) wherein $n = 3$ as described previously in Scheme A, step j.

In step d, the appropriate ω -halo ethylphenylketone compound of structure (6) is halogenated to give the corresponding ω -halo-haloethylphenylketone compound of structure (12) as described previously in step a.

In step e, the appropriate ω -halo tolylketone compound of structure (4) is halogenated to give the corresponding ω -halo halotolylketone compound of structure (13) as described previously in step a.

In step f, the appropriate cyclopropyl ethylphenylketone derivative of structure (7) is halogenated to give the corresponding cyclopropyl haloethylphenylketone compound of structure (14) as described previously in step a.

In step g, the appropriate cyclopropyl tolylketone derivative of structure (5) is halogenated to give the corresponding cyclopropyl halotolylketone of structure (15) as described previously in step a.

In step h, the appropriate cyclopropyl halotolylketone of structure (15) is ring-opened to give the corresponding ω -halo halotolylketone compound of structure (13) wherein $n = 3$ as described previously in Scheme A, step j.

- In step i, the appropriate cyclopropyl haloethylphenylketone compound of structure (14) is ring-opened to give the corresponding ω -halo-
- 5 haloethylphenylketone compound of structure (12) wherein n = 3 as described previously in Scheme A, step j.

- In addition, the novel intermediates of formula (II), formula (III), formula (IV), formula (V), formula (VI) and
- 10 formula (VII) wherein R₅ is OH may be prepared by solvolysis of the corresponding novel intermediates of formula (II), formula (III), formula (IV), formula (V), formula (VI) and formula (VII) wherein R₅ is Cl, Br or I, with, for example, tetrahydrofuran and water or any slightly acidic medium.

15

Starting materials for use in Scheme B are readily available to one of ordinary skill in the art.

- The following examples present typical syntheses as
- 20 described in Scheme B. These examples are understood to be illustrative only and are not intended to limit the scope of the present invention in any way. As used herein, the following terms have the indicated meanings: "g" refers to grams; "mmol" refers to millimoles; "mL" refers to
- 25 milliliters; "bp" refers to boiling point; "°C" refers to degrees Celsius; "mm Hg" refers to millimeters of mercury; "μL" refers to microliters; "μg" refers to micrograms; and "μM" refers to micromolar.

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Example 4

1-[4-(1-Bromo-1-methyl-ethyl)-phenyl]-4-chloro-butan-1-one

Step a, Method A:

- Dissolve 4-chloro-1-(4-isopropyl-phenyl)-butan-1-one (2.10g,
- 35 9.35mmol) in carbontetrachloride (30mL), add N-bromosuccinimide (1.75g, 9.83mmol) and benzoylperoxide (3mg) and stir at reflux for 1 hour. Cool the reaction mixture, filter, wash with water and brine. Dry (MgSO₄), filter and

evaporate the solvent *in vacuo* to give the title compound as an amber oil.

5 Step a, Method B:

- Dissolve 4-chloro-1-(4-isopropyl-phenyl)-butan-1-one (5.00g, 22.2mmol) and N-bromosuccinimide (4.1g, 23.0mmol) in carbon tetrachloride (25mL) and add AIBN radical initiator (300mg). Stir and maintain under a nitrogen atmosphere at 80-90°C or optionally irradiate with a sunlamp until a vigorous exotherm occurs at which point momentarily remove until reflux subsides and then reapply the heat. Reflux for 30 minutes and add another portion of N-bromosuccinimide (100mg) while maintaining reflux and 15 reflux an additional 15 minutes. Cool to room temperature and precipitate the succinimide from the solution by allowing to stand overnight. Filter and wash the succinimide (2.25g) with carbon tetrachloride (20mL). Combine the filtrates and evaporate the solvent *in vacuo* to 20 give the title compound as a yellow oil (6.80g, 100%).

- ¹H NMR (300MHz, CDCl₃) δ 7.935 (d, J=8.4Hz, 2H), 7.70 (d, J=8.4Hz, 2H), 3.66 (t, J=6.3Hz, 2H), 3.16 (t, J=6.8Hz, 2H), 2.21 (p, J=6.8Hz, 2H), 2.19 (s, 6H); ¹³C NMR (75MHz, CDCl₃) 25 δ198.1 (151.63), 135.8, 128.0, 126.0, 62.3, 44.5, 35.3, 35.1, 26.7; IR (neat) 2970, 2910, 1680, 1675, 1600, 1402, 1225, 1180 cm⁻¹.

Step a, Method C:

- 30 Dissolve 4-chloro-1-(4-isopropyl-phenyl)-butan-1-one (74.7g, 333mmol) in methylene chloride (250mL) and add sodium bromate (17.6g, 117mmol) in water (75mL) in a three-necked Morton flask equipped with an overhead stirrer. Cool the solution to 10°C and irradiate with two 150W 35 incandescent flood lamps. Add, by dropwise addition, a solution of sodium bromide (24g, 233mmol) and stir for 2 hours. Illuminate for another 30 minutes, add sodium dithionate (2.0g), separate the organic phase, dry (MgSO₄)

and evaporate the solvent *in vacuo* to give the title compound (100g, 99%).

5 Step a, Method D:

Dissolve 1-[4-(1-bromo-1-methyl-ethyl)-phenyl]-4-chloro-butan-1-one (10.4g assayed at 67% by weight and containing 18wt% 1-[4-(2-propene)-phenyl]-4-chloro-butan-1-one) in methylene chloride (50mL) and sparge hydrogen chloride
10 through the solution for 70 minutes. Evaporate the solvent *in vacuo* to give a 3:1 mixture of 1-[4-(1-bromo-1-methyl-ethyl)-phenyl]-4-chloro-butan-1-one and 1-[4-(1-chloro-1-methyl-ethyl)-phenyl]-4-chloro-butan-1-one (11.6g).

15

Example 5

(4-Bromomethyl-phenyl)-cyclopropyl-methanone

Step g: Dissolve 4-chloro-1-(4-isopropyl-phenyl)-butan-1-one (20g, 124mmol) and 2,2'-Azolons (2-methylpropionitrile)
20 (0.5g) in methylene chloride (100mL) and cool to 5°C. Add a suspension of N-bromosuccinimide (12g) in methylene chloride (50mL) and irradiate with light (150 Watt lamp), maintaining the temperature at 5°C. After 2, 3 and 7 hour time periods, add additional N-bromosuccinimide (6g, 6g,
25 2.8g) and continue stirring. After 7.5 hours, wash with water (200mL) and with 0.4M sodium hydrogen carbonate (2X200mL). Dry (Na₂SO₄), evaporate the solvent *in vacuo* and recrystallize (hexane) to give the title compound as a crystalline solid (26.7g).

30

The following compounds can be prepared by procedures depicted in Scheme B:

[4-(1-bromoethyl)-phenyl]-cyclopropyl-methanone;

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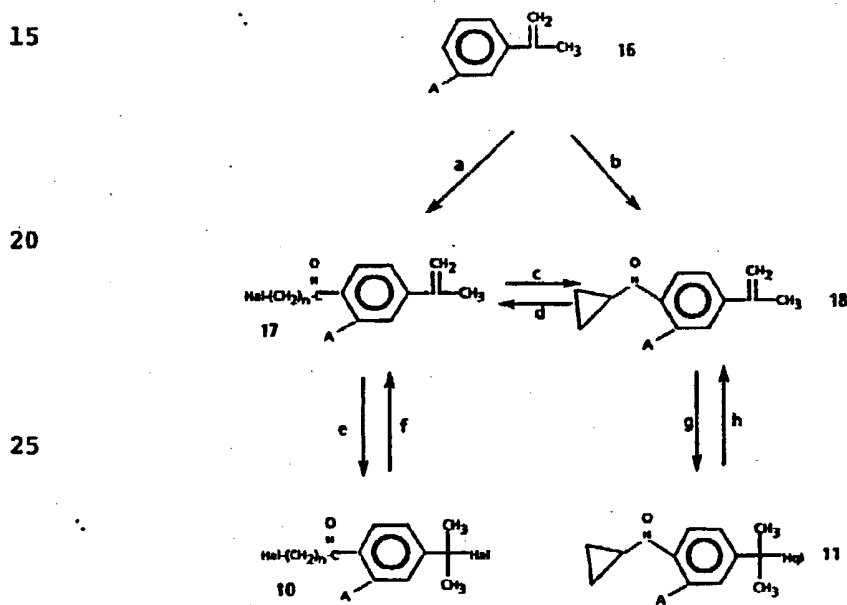
[4-(1-bromo-1-methyl-ethyl)-phenyl]-cyclopropyl-methanone;

1-[4-(1-bromomethyl)-phenyl]-4-chloro-butan-1-one; and

1-[4-(1-bromoethyl)-phenyl]-4-chloro-butan-1-one.

5 The novel intermediates of formula (VIII) and (IX) and
the novel intermediates of formula (II), formula (III),
formula (IV), formula (V), formula (VI) and formula (VII)
wherein R_5 is Cl, Br or I may also be prepared as described
in Scheme C. In Scheme C, all substituents are as
10 previously defined unless otherwise indicated.

Scheme C



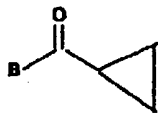
Scheme C provides various general synthetic procedures for preparing the the novel intermediates of formula (VIII) and (IX) and novel intermediates of formula (II), formula 5 (III), formula (IV), formula (V), formula (VI) and formula (VII) wherein R_5 is Cl, Br or I.

In step a, the appropriate α -methylstyrene compound of structure (16) is acylated with an appropriate ω -halo 10 compound of the structure $\text{Hal}-(\text{CH}_2)_n-\text{C}(=\text{O})-\text{B}$, wherein B is Hal or hydroxy, Hal is Cl, Br or I and n is as previously defined to give the corresponding ω -halo- α -methylstyrene compound of structure (17) as described previously in Scheme A, step d.

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In step b, the appropriate α -methylstyrene compound of structure (16) is acylated with an appropriate cyclopropyl compound of the structure

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wherein B is as previously defined to give the 25 corresponding cyclopropyl α -methylstyreneketone derivative of structure (18) as described previously in Scheme A, step e.

In step c, the appropriate ω -halo- α -methylstyrene 30 compound of structure (17) wherein $n = 3$ is ring-closed to give the corresponding cyclopropyl α -methylstyreneketone derivative of structure (18) as described previously in Scheme A, step k.

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In step d, the appropriate cyclopropyl α -methylstyreneketone derivative of structure (18) is ring-opened to give the corresponding ω -halo- α -methylstyrene

compound of structure (17) wherein $n = 3$ as described previously in Scheme A, step j.

5 In step e, the appropriate ω -halo- α -methylstyrene compound of structure (17) is hydrohalogenated to give the corresponding ω -halo-halocumylketone derivative of structure (10).

10 For example, the appropriate ω -halo- α -methylstyrene compound of structure (17) is treated with anhydrous hydrogen halide at a temperature range of from -50°C to room temperature, preferably 0°C -5°C and for a period of time ranging from 5 minutes to 2 hours. The ω -halo-
15 halocumylketone derivative of structure (10) is recovered from the reaction zone by purging with nitrogen.

 In step f, the appropriate ω -halo-halocumylketone derivative of structure (10) is dehydrohalogenated to give
20 the corresponding ω -halo- α -methylstyrene compound of structure (17) by treatment with base as is known in the art.

 In step g, the appropriate cyclopropyl α -
25 methylstyreneketone derivative of structure (18) is hydrohalogenated to give the corresponding cyclopropyl halocumylketone compound of structure (11) as described previously in step e.

30 In step h, the appropriate cyclopropyl halocumylketone compound of structure (11) is dehydrohalogenated to give the corresponding cyclopropyl α -methylstyreneketone derivative of structure (18) as described previously in step f.

The novel intermediates of formula (II), formula (III), formula (IV), formula (V), formula (VI) and formula (VII) wherein R_5 is CN may be prepared as described in Scheme D.

- 5 In Scheme D, all substituents are as previously defined unless otherwise indicated.

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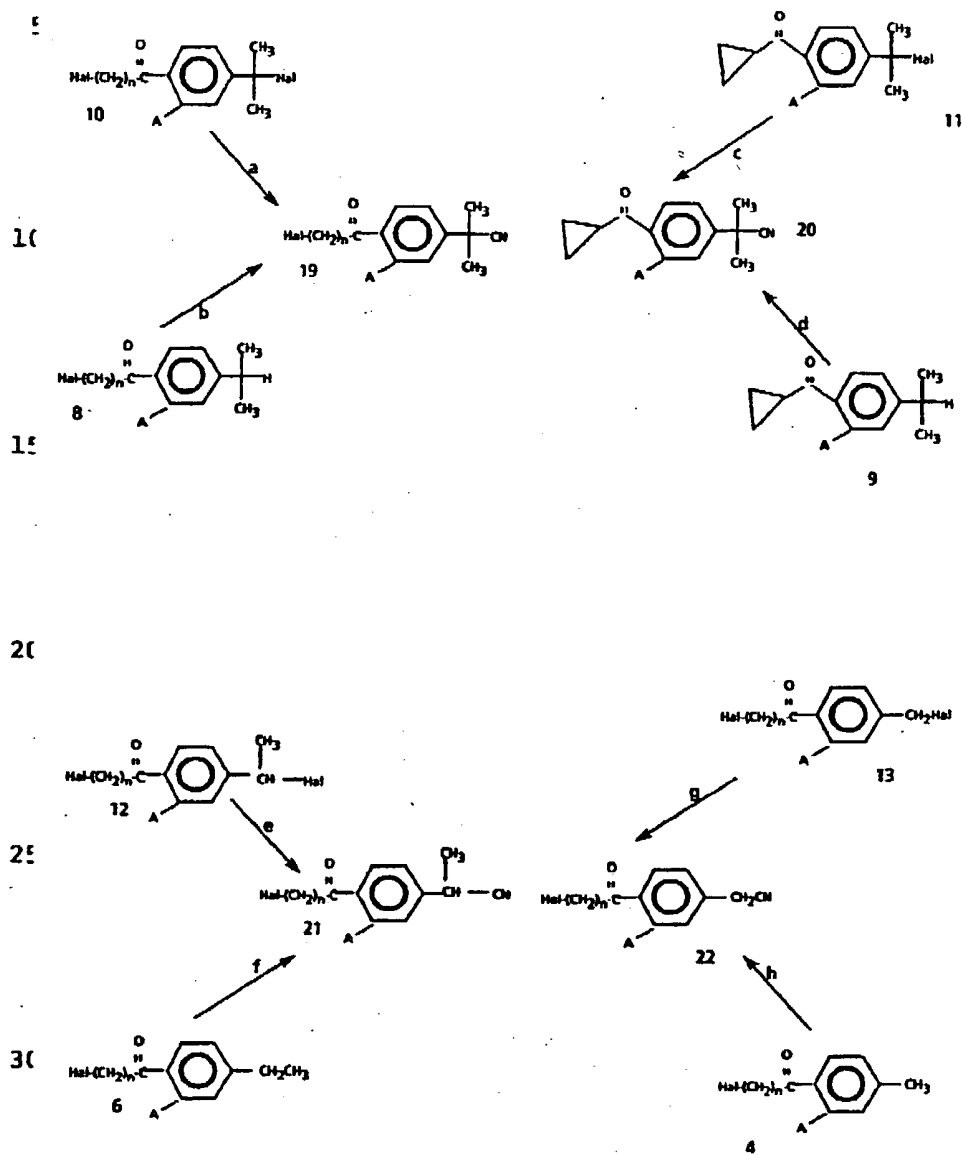
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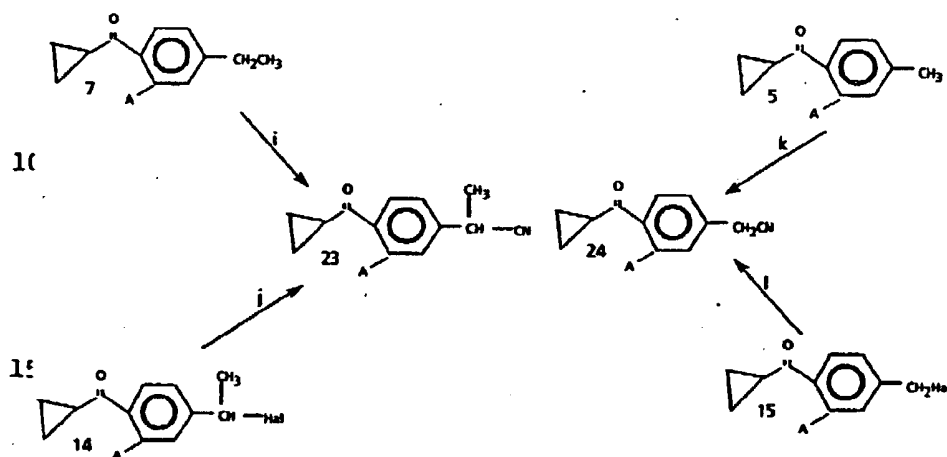
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Scheme D



Scheme D provides various general synthetic procedures for preparing the novel intermediates of formula (II),

Scheme D Cont.



- 20 formula (III), formula (IV), formula (V), formula (VI) and formula (VII) wherein R_5 is CN.

25 In step a, the appropriate ω -halo-halocumylketone compound of structure (10) is cyanated to give the corresponding ω -halo-cyanocumylketone compound of structure (19).

30 For example, the appropriate ω -halo-cyanocumylketone compound of structure (19) may be prepared by reacting an appropriate ω -halo-halocumylketone compound of structure (10) with a suitable cyanating agent. Examples of suitable cyanating agents are trimethylsilyl cyanide, diethylaluminum cyanide and tetrabutylammonium cyanide, with trimethylsilyl cyanide being preferred. The reaction is carried out in a solvent, such as methylene chloride, tetrachloroethane and carbon tetrachloride, with methylene chloride being the preferred solvent. A catalytic amount of a suitable Lewis acid may also be employed in the reaction.

Examples of suitable Lewis acids are boron trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride, with tin tetrachloride being preferred. The reaction time varies from about 1/2 hour to 8 hours, preferably 1/2 to 2 hours and the reaction temperature varies from about 0°C to room temperature, preferably room temperature. The ω -halo-cyanocumylketone compound of structure (16) is recovered from the reaction zone by an aqueous quench followed by extraction as is known in the art. The ω -halo-cyanocumylketone compound of structure (16) may be purified by procedures well known in the art, such as chromatography and crystallization.

15

In step b, the appropriate ω -halo cumylketone compound of structure (8) is cyanated to give the corresponding ω -halo-cyanocumylketone compound of structure (19).

20

For example, the ω -halo-cyanocumylketone compound of structure (19) may be prepared by reacting an appropriate the ω -halo cumylketone compound of structure (8) with a suitable cyanating agent. Examples of suitable cyanating agent are cyanogen chloride, cyanogen bromide and cyanogen iodide, with cyanogen chloride being preferred. The reaction is carried out according to the procedures outlined by Tanner and Bunce, J. Am. Chem. Soc., 91, 3028 (1969).

25

30

In step c, the appropriate cyclopropyl halocumylketone compound of structure (11) is cyanated to give the corresponding cyclopropyl cyanocumylketone compound of structure (20) as described previously in step a.

35

In step d, the appropriate cyclopropyl cumylketone derivative of structure (9) is cyanated to give the corresponding cyclopropyl cyanocumylketone compound of structure (20) as described previously in step b.

In step e, the appropriate ω -halo-haloethylphenylketone compound of structure (12) is cyanated to give the
5 corresponding ω -halo-cyanoethylphenylketone compound of structure (21) as described previously in step a.

In step f, the appropriate ω -halo-ethylphenylketone compound of structure (6) is cyanated to give the
10 corresponding ω -halo-cyanoethylphenylketone compound of structure (21) as described previously in step b.

In step g, the appropriate ω -halo halotolylketone compound of structure (13) is cyanated to give the
15 corresponding ω -halo cyanotolylketone compound of structure (22) as described previously in step a.

In step h, the appropriate ω -halo tolylketone compound of structure (4) is cyanated to give the corresponding ω -
20 halo cyanotolylketone compound of structure (22) as described previously in step b.

In step i, the appropriate cyclopropyl ethylphenylketone compound of structure (7) is cyanated to
25 give the corresponding cyclopropyl cyanoethylphenylketone compound of structure (23) as described previously in step b.

In step j, the appropriate cyclopropyl haloethylphenylketone compound of structure (14) is
30 cyanated to give the corresponding cyclopropyl cyanoethylphenylketone compound of structure (23) as described previously in step a.

35 In step k, the appropriate cyclopropyl tolylketone compound of structure (5) is cyanated to give the corresponding cyclopropyl cyanotolylketone compound of structure (24) as described previously in step b.

In step 1, the appropriate cyclopropyl halotolylketone of structure (15) is cyanated to give the corresponding cyclopropyl cyanotolylketone compound of structure (24) as described previously in step a.

Starting materials for use in Scheme D are readily available to one of ordinary skill in the art.

10

The following examples present typical syntheses as described in Scheme D. These examples are understood to be illustrative only and are not intended to limit the scope of the present invention in any way. As used herein, the following terms have the indicated meanings: "g" refers to grams; "mmol" refers to millimoles; "mL" refers to milliliters; "bp" refers to boiling point; "°C" refers to degrees Celsius; "mm Hg" refers to millimeters of mercury; "μL" refers to microliters; "μg" refers to micrograms; and "μM" refers to micromolar.

Example 6

Step a: 2-[4-(4-chloro-butyryl)-phenyl]-2-methyl-propionitrile

25 Dissolve 1-[4-(1-bromo-1-methyl-ethyl)-phenyl]-4-chloro-butan-1-one (2.00g, 6.59mmol) in anhydrous methylene chloride (20mL) and place under an argon atmosphere. Add trimethylsilyl cyanide (1.10mL, 8.25mmol) followed by tin (IV) chloride (0.20mL, 1.7mmol) via syringe. Stir at reflux
30 for 1 hour, add water (20mL) and stir for an additional 1/2 hour. Separate the layers and extract the aqueous layer with methylene chloride. Combine the organic layers, wash with brine, dry (MgSO₄), filter and evaporate the solvent *in vacuo*. Purify by silica gel chromatography (15% ethyl
35 acetate/hexane) to give the title compound as a white solid; mp 79-80°C.

Example 7

Step 1: (4-Cyclopropanecarbonyl-phenyl)-acetonitrile

Mix (4-bromomethyl-phenyl)-cyclopropyl-methanone (5.0g, 21mmol), potassium cyanide (2.0g, 30mmol), tetra-
5 butylammonium bromide (150mg), water (5mL) and acetonitrile (50mL). Mechanically stir at room temperature for 3 hours, pour into water (450mL) and stir overnight. Collect by filtration and recrystallize (hexane) to give the title compound as a white crystalline solid; mp 86-87°C.

10

The following compounds can be prepared by the synthetic procedures depicted in Scheme D:

15 2-(4-Cyclopropanecarbonyl-phenyl)-propionitrile;

2-(4-Cyclopropanecarbonyl-phenyl)-2-methyl-propionitrile;

[4-(4-Chloro-butyryl)-phenyl]-acetonitrile; and

20

2-[4-(4-Chloro-butyryl)-phenyl]-propionitrile.

25

30

35

The novel intermediates of formula (II), formula (III), formula (IV), formula (V), formula (VI) and formula (VII) wherein R_5 is CN may also be prepared as described in Scheme E. In Scheme E, all substituents are as previously defined unless otherwise indicated.

Scheme E

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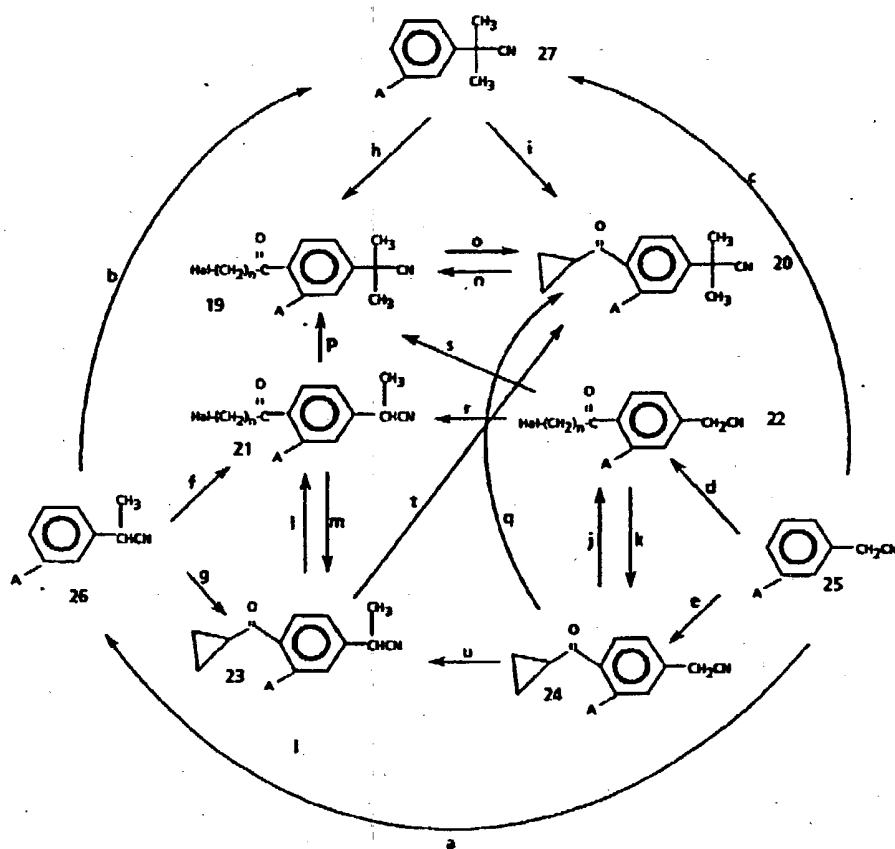
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Scheme E provides alternative various general synthetic procedures for preparing the novel intermediates of formula

(II), formula (III), formula (IV), formula (V), formula (VI) and formula (VII) wherein R₅ is CN.

5 In step a, the appropriate phenylacetonitrile compound of structure (25) is methylated to give the corresponding 2-cyanoethylbenzene compound of structure (26) as described previously in Scheme A, step a.

10 Appropriate phenylacetonitrile compounds of structure (25) may be prepared from the corresponding benzyl halide by techniques and procedures well known by one of ordinary skill in the art and described previously in Scheme D, step a.

15 Appropriate benzyl halide compounds may be prepared from the corresponding toluene derivative of structure (1) as described previously in Scheme B, step a.

20 In step b, the appropriate 2-cyanoethylbenzene compound of structure (26) is methylated to give the corresponding 2-cyano-2-propylbenzene compound of structure (27) as described previously in Scheme A, step a.

25 Appropriate 2-cyanoethylbenzene compound of structure (26) may be prepared from the corresponding α -methylbenzyl halide by techniques and procedures well known by one of ordinary skill in the art and as described previously in step a.

30 Appropriate α -methylbenzyl halide compounds may be prepared from the corresponding ethylbenzene derivative of structure (2) as described previously in Scheme B, step a.

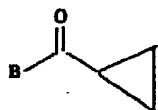
35 In step c, the appropriate phenylacetonitrile compound of structure (25) is dimethylated to give the corresponding 2-cyano-2-propylbenzene compound of structure (27) as described previously in Scheme A, step c.

In step d, the appropriate phenylacetonitrile compound of structure (25) is acylated with an appropriate ω -halo compound of the structure $\text{Hal}-(\text{CH}_2)_n-\text{C}(=\text{O})-\text{B}$, wherein B is Hal or hydroxy, Hal is Cl, Br or I and n is as previously defined to give the corresponding ω -halo cyanotolylketone compound of structure (22) as described previously in Scheme A, step d.

10

In step e, the appropriate phenylacetonitrile compound of structure (25) is acylated with an appropriate cyclopropyl compound of the structure

15



wherein B is as previously defined to give the corresponding cyclopropyl cyanotolylketone compound of structure (24) as described previously in Scheme A, step e.

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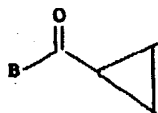
In step f, the appropriate 2-cyanoethylbenzene compound of structure (26) is acylated with an appropriate ω -halo compound of the structure $\text{Hal}-(\text{CH}_2)_n-\text{C}(=\text{O})-\text{B}$, wherein B is Hal or hydroxy, Hal is Cl, Br or I and n is as previously defined to give the corresponding ω -halo-cyanoethylphenylketone compound of structure (21) as described previously in Scheme A, step d.

25

30

In step g, the appropriate 2-cyanoethylbenzene compound of structure (26) is acylated with an appropriate cyclopropyl compound of the structure

35



wherein B is as previously defined to give the corresponding cyclopropyl cyanoethylphenylketone compound of structure (23) as described previously in Scheme A, step

5. e.

In step h, the appropriate 2-cyano-2-propylbenzene compound of structure (27) is acylated with an appropriate ω -halo compound of the structure $\text{Hal}-(\text{CH}_2)_n-\text{C}(=\text{O})-\text{B}$, wherein
10 B is Hal or hydroxy, Hal is Cl, Br or I and n is as previously defined to give the corresponding ω -halo-cyanocumylketone compound of structure (19) as described previously in Scheme A, step d.

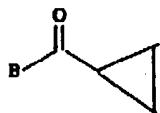
15 Appropriate 2-cyano-2-propylbenzene compound of structure (27) may be prepared from the corresponding α,α -dimethylbenzyl halide by techniques and procedures well known by one of ordinary skill in the art and as described previously in step a.

20

Appropriate α,α -dimethylbenzyl halide compounds may be prepared from the corresponding cumene derivative of structure (3) as described previously in Scheme B, step a.

25 In step i, the appropriate 2-cyano-2-propylbenzene compound of structure (27) is acylated with an appropriate cyclopropyl compound of the structure

30



wherein B is as previously defined to give the corresponding cyclopropyl cyanocumylketone compound of
35 structure (20) as described previously in Scheme A, step e.

In step j, the cyclopropyl functionality of the appropriate cyclopropyl cyanotolylketone compound of

structure (24) is ring-opened to give the corresponding ω -halo cyanotolylketone compound of structure (22) wherein $n = 3$ as described previously in Scheme A, step j.

5

In step k, the appropriate ω -halo cyanotolylketone compound of structure (22) wherein $n = 3$ is ring-closed to give the corresponding cyclopropyl cyanotolylketone compound of structure (24) as described previously in

10 Scheme A, step k.

In step l, the cyclopropyl functionality of the appropriate cyclopropyl cyanoethylphenylketone compound of structure (23) is ring-opened to give the corresponding ω -halo-cyanoethylphenylketone compound of structure (21) wherein $n = 3$ as described previously in Scheme A, step j.

In step m, the appropriate ω -halo-cyanoethylphenylketone compound of structure (21) wherein $n = 3$ is ring-closed to give the corresponding cyclopropyl cyanoethylphenylketone compound of structure (23) as described previously in Scheme A, step k.

In step n, the cyclopropyl functionality of the appropriate cyclopropyl cyanocumylketone compound of structure (20) is ring-opened to give the corresponding ω -halo-cyanocumylketone compound of structure (19) wherein $n = 3$ as described previously in Scheme A, step j.

In step o, the appropriate ω -halo-cyanocumylketone compound of structure (19) is ring-closed to give the corresponding cyclopropyl cyanocumylketone compound of structure (20) as described previously in Scheme A, step k.

In step p, the appropriate ω -halo-cyanoethylphenylketone compound of structure (21) is methylated to give the corresponding ω -halo-

cyanocumylketone compound of structure (19) as described previously in Scheme A, step a.

5 In step q, the appropriate cyclopropyl cyanotolylketone compound of structure (24) is dimethylated to give the corresponding cyclopropyl cyanocumylketone compound of structure (20) as described previously in Scheme A, step c.

10 In step r, the appropriate ω -halo cyanotolylketone compound of structure (22) is methylated to give the corresponding ω -halo-cyanoethylphenylketone compound of structure (21) as described previously in Scheme A, step a.

15 In step s, the appropriate ω -halo cyanotolylketone compound of structure (22) is dimethylated to give the corresponding ω -halo-cyanocumylketone compound of structure (19) as described previously in Scheme A, step c.

20 In step t, the appropriate cyclopropyl cyanoethylphenylketone compound of structure (23) is methylated to give the corresponding cyclopropyl cyanocumylketone compound of structure (20) as described previously in Scheme A, step a.

25 In step u, the appropriate cyclopropyl cyanotolylketone compound of structure (24) is methylated to give the corresponding cyclopropyl cyanoethylphenylketone compound of structure (23) as described previously in Scheme A, step
30 a.

Starting materials for use in Scheme E are readily available to one of ordinary skill in the art.

35 The following examples present typical syntheses as described in Scheme E. These examples are understood to be illustrative only and are not intended to limit the scope of the present invention in any way. As used herein, the

following terms have the indicated meanings: "g" refers to grams; "mmol" refers to millimoles; "mL" refers to milliliters; "bp" refers to boiling point; "°C" refers to degrees Celsius; "mm Hg" refers to millimeters of mercury; "µL" refers to microliters; "µg" refers to micrograms; and "µM" refers to micromolar.

Example 7

10 Step c: Cumyl cyanide

Place phenylacetonitrile (92.3mL, 0.800mol), tetra n-butylammonium chloride (4.45g of a 50% solution, 8.0mmol) and 50% aqueous sodium hydroxide solution (2.874 mole NaOH) into a 3-neck round-bottom flask, with a thermowell, 15 overheard stirrer, reflux condenser with a dry-ice/acetone trap and a sparge tube. Heat to 40-70C with stirring at 115 RPM (paddle stir blade), and bubble in methyl chloride gas (11.7g, 0.232 mole) over a 30 minute period. Turn off the methyl chloride addition and heat and stir overnight.

20

Sparge additional methyl chloride (35.4g, 0.700 mol) into the reaction mixture (heated to 35C) over a period of 2 hours. Stir the resulting mixture at ambient temperature for 22 hours and sparge additional methyl chloride (39.5g, 25 0.781mol) into the reaction mixture at a temperature of 40-70C (mostly at 55-60C). Sparge additional methyl chloride (8.7g, 0.172mol) into the reaction mixture and allow to cool to 30C. Remove the condenser and add deionized water (250mL) and heptane (250mL). Transfer to a separatory 30 funnel and draw off the aqueous (bottom) layer. Wash the remaining organic layer with fresh water (2X100mL), evaporate the solvent in vacuo to give a dark red oil.

Add the oil, 50% aqueous sodium hydroxide (79g, 0.988 mole) 35 and tetra n-butylammonium chloride (1.0g, 3.6mmol) to a 500mL 3-necked round bottom flask with a magnetic stir bar. Using the same experimental procedure described above, sparge in methyl chloride. Heat to 40-60C, stir and sparge in methyl chloride (20.5g, 0.40 mole) over 1 hour. Allow

- the reaction mixture to cool, add deionized water (100g) and stir. Allow the layers to settle and remove the bottom layer by pipet. Repeat wash with additional water (100g) to give the title compound as a dark orange oil (111.0g, wet with water).

Example 8

- Step g: 2-(4-Cyclopropanecarbonyl-phenyl)-2-methyl-
10 propionitrile
Dissolve potassium t-butoxide (2.42g, 21.6mmol) in diglyme (8mL), cool to 10°C and slowly add with mechanical stirring, a solution of (4-cyclopropanecarbonyl-phenyl)-acetonitrile (2g, 10.8mmol) and methyl iodide (1.5mL, 15 24.0mmol) in diglyme (10mL). After 10 minutes, add additional potassium t-butoxide (0.3g, 2.6mmol) in diglyme (2mL) and stir for a total of 45 minutes. Pour into a mixture of water (100mL) and ethyl acetate (50mL) and adjust the pH to 1.5-2 with dilute hydrochloric acid.
20 Separate the organic phase and extract the aqueous phase with ethyl acetate (50mL). Combine the organic phases and wash with brine (2X100mL). Dry (Na₂SO₄), evaporate the solvent *in vacuo* and recrystallize (ethyl ether/hexane) to give the title compound as a yellow solid; mp 80-82°C.

25

The following compounds can be prepared by procedures depicted in Scheme E:

- (4-Cyclopropanecarbonyl-phenyl)-acetonitrile;
30 2-[4-(4-chloro-butyryl)-phenyl]-2-methyl-propionitrile;
2-(4-Cyclopropanecarbonyl-phenyl)-propionitrile;
35 [4-(4-Chloro-butyryl)-phenyl]-acetonitrile; and
2-[4-(4-Chloro-butyryl)-phenyl]-propionitrile.

The novel intermediates of formula (II), formula (III), formula (IV), formula (V), formula (VI) and formula (VII) wherein R_5 is COOalkyl may also be prepared as described in Scheme F. In Scheme F, all substituents are as previously defined unless otherwise indicated.

Scheme F

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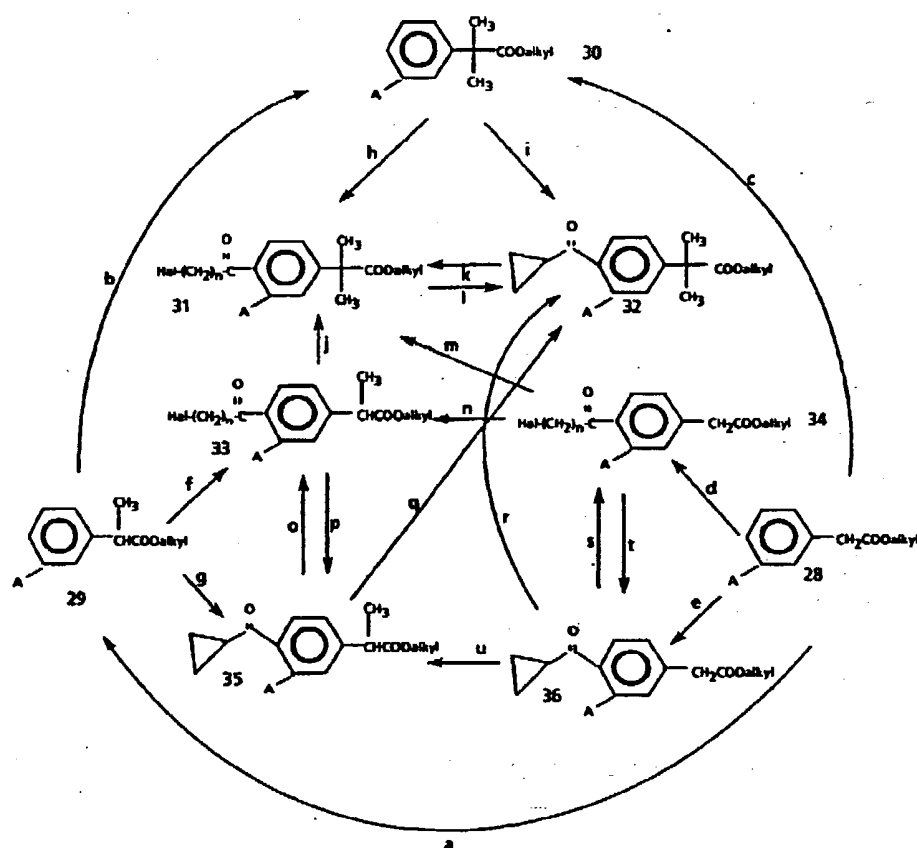
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Scheme F provides alternative various general synthetic procedures for preparing the novel intermediates of formula (II), formula (III), formula (IV), formula (V), formula (VI) and formula (VII) wherein R₅ is COOalkyl.

In step a, the appropriate phenylacetic acid ester compound of structure (28) is methylated to give the corresponding α -methylphenylacetic acid ester compound of structure (29) as described previously in Scheme A, step a.

Appropriate phenylacetic acid ester compounds of structure (28) are prepared from the corresponding phenylacetic acid compounds by standard esterification reactions which are well known by one of ordinary skill in the art.

Appropriate phenylacetic acid compounds may be prepared by hydrolysis of the corresponding phenylacetonitrile compounds of structure (25) by techniques and procedures well known and appreciated by one of ordinary skill in the art, such as base hydrolysis. Alternatively, the phenylacetic acid compounds may be prepared by electrochemical carboxylation of the corresponding benzyl halide as described in Scheme H, step h.

In step b, the appropriate α -methylphenylacetic acid ester compound of structure (29) is methylated to give the corresponding α,α -dimethylphenylacetic acid ester compound of structure (30) as described previously in Scheme A, step a.

Alternatively α -methylphenylacetic acid ester compound of structure (29) are prepared for the corresponding α -methylphenylacetic acid compounds by standard esterification reactions which are well known by one of ordinary skill in the art as described in step a.

Appropriate α -methylphenylacetic acid compounds may be prepared by hydrolysis of the corresponding 2-cyanoethylbenzene compound of structure (26) as described previously in step a. Alternatively, the α -methylphenylacetic acid compounds may be prepared by electrochemical carboxylation of the corresponding α -methylbenzyl halide as described in Scheme H, step h.

10 In step c, the appropriate phenylacetic acid ester compound of structure (28) is dimethylated to give the corresponding α,α -dimethylphenylacetic acid ester compound of structure (30) as described previously in Scheme A, step c.

15 Alternatively α,α -dimethylphenylacetic acid ester compound of structure (30) are prepared for the corresponding α,α -dimethylphenylacetic acid compounds by standard esterification reactions which are well known by one of ordinary skill in the art as described in step a.

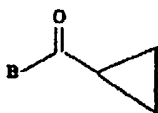
Appropriate α,α -dimethylphenylacetic acid compounds may be prepared by hydrolysis of the corresponding 2-cyano-2-propylbenzene compound of structure (27) as described previously in step a. Alternatively, the α,α -dimethylphenylacetic acid compounds may be prepared by electrochemical carboxylation of the corresponding α,α -dimethylbenzyl halide as described in Scheme H, step h. Appropriate α,α -dimethylbenzyl halide compounds may be prepared by hydrohalogenation of the corresponding α -methylstyrene as described previously in Scheme C, step e.

In step d, the appropriate phenylacetic acid ester compound of structure (28) is acylated with an appropriate ω -halo compound of the structure $\text{Hal}-(\text{CH}_2)_n-\text{C}(=\text{O})-\text{B}$, wherein B is Hal or hydroxy, Hal is Cl, Br or I and n is as previously defined to give the corresponding ω' -halo- α' -

keto-phenylacetic acid ester compound of structure (34) as described previously in Scheme A, step d.

- 5 In step e, the appropriate phenylacetic acid ester compound of structure (28) is acylated with an appropriate cyclopropyl compound of the structure

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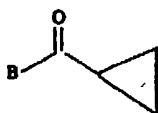
- wherein B is as previously defined to give the corresponding cyclopropylketo-phenylacetic acid ester compound of structure (33) as described previously in Scheme A, step e.

- 15 In step f, the appropriate α -methylphenylacetic acid ester compound of structure (26) is acylated with an appropriate ω -halo compound of the structure $\text{Hal}-(\text{CH}_2)_n-\text{C}(=\text{O})-\text{B}$, wherein B is Hal or hydroxy, Hal is Cl, Br or I and n is as previously defined to give the corresponding ω' -halo- α' -keto- α -methylphenylacetic acid ester compound of structure (30) as described previously in Scheme A, step d.

25

- In step g, the appropriate α -methylphenylacetic acid ester compound of structure (29) is acylated with an appropriate cyclopropyl compound of the structure

30



- wherein B is as previously defined to give the corresponding cyclopropylketo- α -methylphenylacetic acid ester compound of structure (35) as described previously in Scheme A, step e.

35

In step h, the appropriate α,α -dimethylphenylacetic acid ester compound of structure (30) is acylated with an appropriate ω -halo compound of the structure $\text{Hal}-(\text{CH}_2)_n-\text{C}(=\text{O})-\text{B}$, wherein B is Hal or hydroxy, Hal is Cl, Br or I and n is as previously defined to give the corresponding ω' -halo- α' -keto- α,α -di-methylphenylacetic acid ester compound of structure (31) as described previously in Scheme A, step d.

10

Appropriate α,α -dimethylphenylacetic acid ester compound of structure (30) are prepared for the corresponding α,α -dimethylphenylacetic acid compounds by standard esterification reactions which are well known by one of ordinary skill in the art as described in step a.

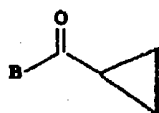
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Appropriate α,α -dimethylphenylacetic acid compounds may be prepared by hydrolysis of the corresponding 2-cyano-2-propylbenzene compound of structure (27) as described previously in step a.

20

In step i, the appropriate α,α -dimethylphenylacetic acid ester compound of structure (30) is acylated with an appropriate cyclopropyl compound of the structure

25



wherein B is as previously defined to give the corresponding cyclopropylketo- α,α -dimethylphenylacetic acid ester compound of structure (32) as described previously in Scheme A, step e.

30

In step j, the appropriate ω' -halo- α' -keto- α,α -methylphenylacetic acid ester compound of structure (33) is methylated to give the corresponding ω' -halo- α' -keto- α,α -

35

di-methylphenylacetic acid ester compound of structure (32) as described previously in Scheme A, step a.

- 5 In step k, the cyclopropyl functionality of the appropriate cyclopropylketo- α,α -dimethylphenylacetic acid ester compound of structure (32) is ring-opened to give the corresponding ω' -halo- α' -keto- α,α -di-methylphenylacetic acid ester compound of structure (31) wherein $n = 3$ as
10 described previously in Scheme A, step j.

- In step l, the appropriate ω' -halo- α' -keto- α,α -di-methylphenylacetic acid ester compound of structure (31) wherein $n = 3$ is ring-closed to give the corresponding
15 cyclopropylketo- α,α -dimethylphenylacetic acid ester compound of structure (32) as described previously in Scheme A, step k.

- In step m, the appropriate ω' -halo- α' -keto-phenylacetic
20 acid ester compound of structure (34) is dimethylated to give the corresponding ω' -halo- α' -keto- α,α -di-methylphenylacetic acid ester compound of structure (31) as described previously in Scheme A, step c.

- 25 In step n, the appropriate ω' -halo- α' -keto-phenylacetic acid ester compound of structure (34) is methylated to give the corresponding ω' -halo- α' -keto- α -methylphenylacetic acid ester compound of structure (33) as described previously in Scheme A, step a.

- 30 In step o, the cyclopropyl functionality of the appropriate cyclopropylketo- α -methylphenylacetic acid ester compound of structure (35) is ring-opened to give the corresponding ω' -halo- α' -keto- α -methylphenylacetic acid
35 ester compound of structure (33) wherein $n = 3$ as described previously in Scheme A, step j.

In step p, the appropriate ω' -halo- α' -keto- α -methylphenylacetic acid ester compound of structure (33) wherein $n = 3$ is ring-closed to give the corresponding
5 cyclopropylketo- α -methylphenylacetic acid ester compound of structure (35) as described previously in Scheme A, step k.

In step q, the appropriate cyclopropylketo- α -methylphenylacetic acid ester compound of structure (35) is
10 methylated to give the corresponding cyclopropylketo- α,α -dimethylphenylacetic acid ester compound of structure (32) as described previously in Scheme A, step a.

In step r, the appropriate cyclopropylketo-phenylacetic
15 acid ester compound of structure (36) is dimethylated to give the corresponding cyclopropylketo- α,α -dimethylphenylacetic acid ester compound of structure (32) as described previously in Scheme A, step c.

20 In step s, the cyclopropyl functionality of the appropriate cyclopropylketo-phenylacetic acid ester compound of structure (36) is ring-opened to give the corresponding ω' -halo- α' -keto-phenylacetic acid ester compound of structure (34) wherein $n = 3$ as described
25 previously in Scheme A, step j.

In step t, the appropriate ω' -halo- α' -keto-phenylacetic acid ester compound of structure (34) wherein $n = 3$ as is ring-closed to give the corresponding cyclopropylketo-
30 phenylacetic acid ester compound of structure (36) as described previously in Scheme A, step k.

In step u, the appropriate cyclopropylketo-phenylacetic acid ester compound of structure (36) is methylated to give
35 the corresponding cyclopropylketo- α -methylphenylacetic acid ester compound of structure (35) as described previously in Scheme A, step a.

Starting materials for use in Scheme F are readily available to one of ordinary skill in the art.

5 The following examples present typical syntheses as described in Scheme F. These examples are understood to be illustrative only and are not intended to limit the scope of the present invention in any way. As used herein, the following terms have the indicated meanings: "g" refers to
10 grams; "mmol" refers to millimoles; "mL" refers to milliliters; "bp" refers to boiling point; "°C" refers to degrees Celsius; "mm Hg" refers to millimeters of mercury; "μL" refers to microliters; "μg" refers to micrograms; and "μM" refers to micromolar.

15

Example 9

Step c: 2-Methyl-2-phenylpropionate, methyl ester

Equip a two liter, 3-necked, round bottom flask with a thermowell with a thermometer, heating mantle, mechanical
20 agitator, gas inlet for MeCl, rubber septum for sampling by syringe and a cryoscopic condensing system. The condensing system is composed of an 18 inch inner helical coil/outer jacket condenser chilled to -50C with refrigerated acetone topped with a dry ice cold finger having approximately 100
25 square inches of chilled surface area. The cold finder is vented through a drying tube filled with drying agent and MeCl is supplied from a lecture bottle mounted on a digital balance. The feed rate can be accurately controlled using a needle valve and monitored by rotomter. The rotometer is
30 calibrated with MeCl to give an average response of 2.5mg/min/scale division. Phenylacetic acid, ethyl ester is supplied via 1/16 inch stainless steel tubing inserted through the rubber sampling septum by a HPLC pump from a 1 liter bottle mounted on a digital balance. The bottle is
35 sealed with a septum and vented through a drying tube filled with drying agent. The temperature is controlled using a thermowatch to regulate the heating mantle. If cooling is required, it is accomplished either by immersing

-76-

the reaction flask in a water bath or simply by removing the mantle.

- 5 The phenylacetic acid, ethyl ester pump is primed with phenylacetic acid, ethyl ester balance is zeroed. The MeCl balance is zeroed and a 200g sample of 60% NaH is weighed into a wide mouth plastic jar in a nitrogen filled glove bag and is transferred to the reaction vessel through a funnel (sampling septum is removed). Through the same funnel is added anhydrous glyme (800mL) and the septum (pierced by the 1/16 inch phenylacetic acid, ethyl ester feed tube) is replaced. The mixture is agitated and heated 15 to 50C while MeCl (40g) is introduced. When the reaction mixture reaches 50C, the continuous addition of phenylacetic acid, ethyl ester/t-butanol at 1 mL/min and MeCl at approximately 0.62g/min. is initiated. Samples of about 20 p.l mL are withdrawn at intervals using a disposable syringe fitted with an 8 inch needle. A portion of the sample (5-15 drops depending on the accumulation of product) is dissolved in 25% aqueous acetonitrile (5mL) and analyzed immediately. The reaction is continued for an additional 2 hours at 50C and then at ambient temperature 25 overnight.

In the apparatus described above, agitate NaH (180g of 60%) and anhydrous glyme (800mL) and heat to 50C. Add MeCl (52g) along with methyl phenylacetate (20g). Stir for 1 hour at 50C, then add, by continuous addition, methyl phenylacetate (0.8mL/min) and MeCl (approximately 0.53g/min). Stir for 1 hour, stop the additions and continue heating for 1.5 hours. Resume the additions and run for 45 minutes. Allow to agitate at ambient temperature overnight. Heat the reaction to 50C and resume the addition of methyl phenylacetate (0.4mL/min) and MeCl (approximately 0.27g/min). When a total of 246g of methyl phenylacetate has been added, stop the addition and agitate

- overnight. Distill the glyme at 1 atm. until the pot temperature reaches 125°C. Cool the residue and pour into water (1L) containing acetic acid (100mL). Filter through
- 5 filter aid and separate the phases. Distill the organic phase through a 10-plate Oldershaw column fitted with a reflux splitting head at 4mm Hg. Collect 10mL at a 5:2 reflux ratio and discard. Collect the title compound at a 2:1 reflux ratio and head temperature of 93°C (100g).

10

Example 10

Step d: [4-(4-Chloro-butyl)-phenyl]-acetic acid, ethyl ester and [3-(4-Chloro-butyl)-phenyl]-acetic acid, ethyl ester

- 15 Method A: Load a 3-neck flask with sublimed AlCl_3 (293g, 2.08mmol) and heptane (400mL). Cool to below 5°C and slowly add chlorobutyl chloride (125mL), keeping the temperature below 5°C. Add phenylethyl acetate (160mL), keeping the temperature below 10°C and stir overnight.
- 20 Decant the heptane layer and dissolve the residue in methylene chloride (400mL). Slowly pour the methylene chloride solution into a mixture of concentrated hydrochloric acid (200mL) and cracked ice. Separate the organic phase, wash with water (1L), followed by 5% sodium
- 25 hydrogen carbonate (1L). Evaporate the solvent *in vacuo* to give a red oil (243g).

- Dissolve the red oil (243g) in methylene chloride (250mL) and sparge with hydrogen chloride gas for 1.5 hours and
- 30 evaporate the solvent *in vacuo* to give the title compound as a 50:50 mixture of para and meta isomers (243g).

- Method B: Place aluminum chloride (293g) and methylene chloride (300mL) in a 1L, 3-neck round bottom flask with a
- 35 thermowell and equipped with a thermometer, mechanical stirrer, reflux condenser, equilibrating dropping funnel and ice bath. Cool to 10°C and add, by dropwise addition, 4-chlorobutyl chloride (169g), keeping the temperature

below 10C. After addition is complete, add, by dropwise addition, phenylethyl acetate (164g), keeping the temperature below 10C. Heat the reaction to 40C for 16 hours, slowly pour into a mechanically agitated 4L beaker containing ice/water (2000g) and stir for 1 hour. Separate the layers, extract the water phase with methylene chloride (50mL), filter the combined organic phases through a 1/4 inch thick bed of filter aid and extract sequentially with water (100mL) and 10 wt% Na₂CO₃ (200mL). Re-extract the carbonate solution with fresh methylene chloride (50mL) and wash the combined methylene chloride solutions with water (100mL). Distill off solvent at atmospheric pressure until the pot temperature reaches 120C. Cool the residue and dilute with 2B absolute ethanol (200mL). Heat the solution to 70C and sparge in anhydrous HCl (20g) over 10 minutes. After 40 minutes, cool the reaction and hold overnight under nitrogen. Evaporate the solvent in vacuo to give the title compound (258g).

20

Example 11

Step k: 2-[4-(4-Chloro-butyl)-phenyl]-2-methyl-propionic acid, ethyl ester

25 Method A: Dissolve 2-(4-cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester (100g) in xylene (500mL) and ethanol (100mL) and heat to 70°C. Sparge the atmosphere of the reaction with hydrogen chloride gas (24.6g) over 220 hours. Evaporate the solvent *in vacuo* to give the title compound.

35 Method B: Add a solution of 5M HCl in acetonitrile (50mL, 9g of HCl, 247mmol) to 2-(4-cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester (25.5g, 98mmol) and seal in a 100mL flask with a rubber septum. Heat to 50°C for 4 hours, dilute with toluene (50mL), wash with water (50mL), aqueous 10% Na₂CO₃ (50mL) and then water (50mL). Evaporate the solvent *in vacuo* to give the title compound as an oil

(27.2g).

Method C: Place 2-(4-cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester (86g, 330mmol) and dry acetonitrile (70mL) in a 250mL 3-neck round-bottom flask equipped with a magnetic stirbar, thermometer, gas inlet and distillation head connected to a balloon by way of a T fitting for pressure control. Slowly warm the reaction mixture with stirring to 60°C while sparging excess HCl into the reaction mixture for 6 hours, dilute with toluene (50mL), wash with water (50mL), aqueous 10% Na₂CO₃ (50mL) and then water (50mL). Evaporate the solvent *in vacuo* to give the title compound.

15

Method D: Place 2-(4-cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester (91g, 350mmol) in a 1 L 3-neck round-bottom flask equipped with a magnetic stirbar, thermometer, gas inlet, and distillation head connected to a balloon by way of a T fitting for pressure control. Slowly sparge in anhydrous HCl, keeping the balloon slightly inflated. After 10 minutes, add acetonitrile (590mL), heat to 65°C and add excess HCl over 7 hours. Heat the mixture and remove acetonitrile/HCl overhead. After 500mL of acetonitrile is removed, add mixed xylene (200mL) and continue the distillation. Add additional xylene (200m) and after a total of 640mL of solvent has been removed (pot = 130°C and overhead = 130°C), add ethanol 2B (100mL). Remove the ethanol by distillation to give the title compound as a oil (330g).

Method E: Place 2-(4-cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester (98g, 410mmol) and xylenes (600mL) in a 1L 3-neck round-bottom flask equipped with a magnetic stirbar, thermometer, gas inlet and distillation head connected to a balloon by way of a T fitting for pressure control. Heat the reaction mixture to 80°C and slowly sparge in anhydrous HCl. After 100

minutes, add ethanol 2B (100mL) and HCl (26g) and heat to 35°C for 2 hours. Remove the ethanol and HCl by distillation with aspirator vacuum (pot = 35°C, overhead = 5 30°C) to give the title compound as a solution in xylene.

Method F: Place 2-(4-cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester (500g) in a 4L Hastelloy reactor equipped with a gas inlet, overhead stirrer, 10 temperature control and dip pipe for sampling. Heat the oil to 60C and evacuate the head space. Add HCl raising the pressure to 10psig and react for 80-300 minutes. Vent the excess HCl and sparge the oil with nitrogen for 5 minutes to give the title compound.

15
Method G: Fit a 2L 3-neck round bottom flask with an overhead paddle stirrer, a gas sparge tube (with fritted end to disperse gas) and a reflux condenser (with drying tube on top, filled with drying agent). Fit the bottom of 20 the flask with a heating mantle and put 2-(4-cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester (78.10g, 0.300 mol), xylenes (400mL) and absolute 2B ethanol (90mL) into the flask. Stir to dissolve all the solids at ambient temperature. Sparge hydrogen chloride 25 from a lecture bottle (38.36g, 1.052 mol) into the stirred solution without external heating over a 15 minute period. Replace the sparge tube with a glass stopper and heat the solution by mantle, with stirring, at 40-79C for 45 minutes and 79C for 15 minutes. Replace the reflux condenser with 30 a simple still head fitted with a thermometer and condenser. Collect 200 mL of distillate (80-138C at atmospheric pressure) and allow the remaining light yellow solution to cool to give a mixture of the title compound and xylenes.

35

Example

Step t: (4-Cyclopropanecarbonyl-phenyl)-acetic acid, ethyl ester and (3-Cyclopropanecarbonyl-phenyl)-acetic acid, ethyl ester

- 5 Dissolve the mixture of [4-(4-chloro-butyryl)-phenyl]-acetic acid, ethyl ester and [3-(4-chloro-butyryl)-phenyl]-acetic acid, ethyl ester (650g) in 2B ethanol (1250mL). Add, by dropwise addition, a solution of 2B ethanolic KOH (168g in 1000mL), keeping the temperature below 10C. After
10 the addition, stir magnetically for 5 hours at -10C. Bring the mixture to pH 6 with acetic acid (5mL) and filter through a celite pre-coat. Evaporate the solvent in vacuo to give the title compound as an oil (538g).

15 Example 12

Step d: [4-(4-Chloro-butyryl)-phenyl]-acetic acid, 2-ethylhexyl ester

- Mix 2-ethyl-1-hexanol (6.5g, 5mol), triethylamine (50.5g, 0.5mol) and methylene chloride (50mL). Add, by dropwise
20 addition, 2-phenylacetyl chloride (5mol) and warm to 50°C. Stir at room temperature overnight, filter and wash the filtercake with methylene chloride (50mL). Combine the organic phases and wash with 5% aqueous hydrochloric acid (50mL) and water. Dry (MgSO₄), evaporate the solvent in
25 vacuo and purify by distillation to give 2-phenylacetic acid, 2-(2-ethylhexyl) ester.

- Mix chlorobutyryl chloride (16.9g) and AlCl₃ (29.3g) at room temperature. Add 2-phenylacetic acid, 2-ethylhexyl ester
30 (27.6g), keeping the temperature below 10°C. Heat at 35°C for 24 hours, quench in ice water (200g). Separate the organic phase, dry (MgSO₄) and evaporate the solvent in vacuo. Dilute the residue with ethanol (150mL), add hydrogen chloride (5g) and heat to 75°C. After 2.5 hours,
35 add another 5g of hydrogen chloride and stir at 75°C for 24 hours. Evaporate the solvent in vacuo to give the title compound.

-82-

Example 13

Step h: 2-[4-(4-Chloro-butyryl)-phenyl]-2-methyl-propionic acid, ethyl ester and 2-[3-(4-Chloro-butyryl)-phenyl]-2-methyl-propionic acid, ethyl ester

- 5 Place aluminum chloride (58.4g, 438mmol) and methylene chloride (100mL) in a 250 mL 3 neck flask equipped with a condenser, thermometer, and overhead stirrer. Cool to 10C and add, by dropwise addition, ethyl dimethylphenylacetate (40g, 32.4g, 230mmol), keeping the temperature below 10C. Add, by dropwise addition, 4-chlorobutyryl chloride (40g, 208mmol) at 10C. After the addition, slowly warm the mixture to room temperature and then heat at reflux for 15 hours. Quench the reaction into ice (400g) and stir with water (25mL), 10% aqueous sodium carbonate (25mL) and water (25mL). Extract with methylene chloride (2x25mL), wash with (58.7g). Evaporate the solvent in vacuo to give a red oil

- 20 Dissolve the red oil (58.7g) in 2B ethanol (40mL) and place in a 250mL round bottom flask equipped with an overhead stirrer, condenser, thermometer and gas inlet tube. Add anhydrous HCl (3g, 80mmol) with vigorous stirring and heat to 70C for 1 hour. Evaporate the solvent in vacuo to give the title compound as a yellow oil (59g).

Example 14

Step i: 2-(4-Cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester

- 30 Dissolve a mixture of 2-[4-(4-chloro-butyryl)-phenyl]-2-methyl-propionic acid, ethyl ester and 2-[3-(4-chloro-butyryl)-phenyl]-2-methyl-propionic acid, ethyl ester (59g) in 2B ethanol (100mL) and add, by dropwise addition, a solution of KOH (49.4g of 85%) in 2B ethanol (250mL), keeping the temperature below 15C. After the addition, warm the reaction mixture to room temperature and stir magnetically for 1 hour. Bring to pH 6 with acetic acid and filter through a celite pre-coat. Evaporate the

solvent in vacuo to give a mixture of 2-(4-cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester and 2-(3-cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester as an oil (57.1g) Purify by one of the following methods:

Method A: Pack a 31/32 in. I.D. vacuum jacketed and silvered column with 53 inches of 1 in. diameter, 316 stainless steel packing. For high temperature distillation, the column is fitted with an adiabatic jacket composed of an inner layer of 1 in. fiber glass wrapped with heat tape in an upper and lower zone and finally covered with 2 in. fiber glass insulation. The upper zone is heated at 135C and the lower zone at 185C. The magnetic reflux splitting head is controlled by a reflux timer and fitted with a standard thermometer for monitoring overhead temperature. Vacuum is supplied by a system composed of a pump protected by a dry ice trap and fitted with a McLeod gage for monitoring the overhead pressure. The 1L distillation pot is heated with an electric mantle at 65 volts, agitated magnetically and fitted with a mercury manometer for monitoring bottoms pressure, and a thermocouple for monitoring bottoms temperature.

The still pot is charged with 265 g each of m- and p-xylene and fitted with a rubber septum for sampling by syringe. The xylene mixture is heated at total reflux and atmosphere pressure with the temperature 135C at the head and 139C in the bottoms. Samples are withdrawn for analysis by collecting a few drops of distillate and extracting about 1mL from the pot. The still is sampled after 3 hours and again after 18 hours for calibration by GC and theoretical plate calculations using the Fenske correlation and a relative volatility, $\alpha=1.0209$.

Charge the mixture of 2-(4-cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester and 2-(3-

- cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester (901.2g) to the still pot and heat at total reflux until the column has equilibrated. Take a forecut at 2:1
- 5 reflux ratio and increase the reflux ratio to 5:1 and the 2-(3-cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester stripped. Cool and release vacuum and allow to sit overnight. Add bis(2-ethylhexyl)phthalate (dioctyl phthalate) (100mL) to the still pot and restart the still
- 10 as before. Once the still has equilibrated, collect mixed fractions of 2-(4-cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester and 2-(3-cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester at 10:1 reflux ratio. Once the overheads are free of 2-(3-
- 15 cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester by GC analysis, reduce the reflux ratio to 2:1 and collect the title compound.

Method B: Place crude mixture of 2-(4-

- 20 cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester and 2-(3-cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester (4872g) on a rotary evaporator and strip of volatiles to an end point of 85C, 15mm to give a brown oil (4006g). Charge a 3L round bottom three
- 25 neck flask equipped with magnetic stirbar, thermometer and distillation head with stripped crude mixture of 2-(4-cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester and 2-(3-cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester. Distill the oil at 0.5mm Hg
- 30 and discard a light fraction boiling at 25-130C (pot temp - 105-165C, 9.5g). Continue distilling the oil at 0.5mm Hg and collect a second fraction boiling at 130-150C (pot temperature 165-190, 3217g).
- 35 Place the crude flash distilled product (1000g) in a 4L Hastelloy reactor equipped with Camille control along with water (500mL) and ethanol 2B (2L). Heat the mixture to 40C while agitating at 400 rpm. Set the reactor jacket to cool

the contents at approximately 12C/hour to a final temperature of 0C after a clear solution is observed. Then set the jacket to cool the reactor contents at

5 approximately 12C/hour to a final temperature of -15C and hold at that temperature for more than one hour. Filter the slurry, wash with cold (-15C) ethanol, cold heptanes (-15C) and dry to give a solid (507g). Purify by recrystallization from mixed heptanes as above to give the

10 title compound (503g) after drying.

Example 15

Step h and step i: 2-(4-Cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester and 2-(3-

15 Cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester

Method A: Place aluminum chloride (586g, 4.4moles) and methylene chloride (300mL) in a 2L 3-neck round bottom

20 flask equipped with an overhead stirrer, dry ice condenser, and nitrogen atmosphere. Cool to 10C and add, by dropwise addition, chlorobutyl chloride (338g, 2.4moles), keeping the temperature below 15C. After addition is complete, add, by dropwise addition, ethyl 2-methyl-2-

25 phenylpropionate (384g, 2mol), keeping the temperature below 15C. After addition was complete, warm the reaction mixture to 22C and stir for 1 hour. Raise the temperature to 90C, stir for 90 minutes, cool to room temperature and slowly pour into a 6L stirred flask containing ice/water

30 (4kg). Filter through a celite precoat, separate the organic phase and wash the aqueous phase with methylene chloride (50mL). Evaporate the solvent in vacuo to give a mixture of 2-[4-(4-chloro-butyl)-phenyl]-2-methyl-propionic acid, ethyl ester and 2-[3-(4-chloro-butyl)-

35 phenyl]-2-methyl-propionic acid, ethyl ester.

Dissolve the mixture of 2-[4-(4-chloro-butyl)-phenyl]-2-methyl-propionic acid, ethyl ester and 2-[3-(4-chloro-

butyryl)-phenyl]-2-methyl-propionic acid, ethyl ester in 2B ethanol (400mL) and place in a 3L 3-neck round bottom flask equipped with an overhead stirrer, gas inlet and
5 reflux condenser. Add anhydrous HCl (50g) and stir the mixture at 70C for 1 hour. Cool the solution to 15C and add, by dropwise addition, aqueous 50% NaOH (260g), keeping the temperature below 15C. After the addition, stir the mixture an addition 1 hour at 22C. Add toluene (700mL)
10 followed by acetic acid (2g) and then water (500mL). Separate the layers and evaporate the solvent in vacuo to give the title compound as a yellow oil (551g).

Method B: Place aluminum chloride (458g, 3.4mole) and
15 methylene chloride (234mL) in a 2L 3nck round bottom flask equipped with an overhead stirrer, dry ice condenser and nitrogen atmosphere. Cool to 10C and add, by dropwise addition, 4-chlorobutyryl chloride (264g, 1.9mol), keeping the temperature below 15C. After addition is complete,
20 add, by dropwise addition, ethyl 2-methyl-2-phenylpropionate (300g, 1.56mol), keeping the temperature below 15C. After the addition is complete, warm the reaction mixture to 24C and stir for 1 hour. Raise the temperature to 57C for 2 hours, cool to room temperature
25 and slowly pour into a 6L stirred flask containing ice/water (3.1kg). Filter through a celite precoat and separate the phases. Evaporate the solvent in vacuo to give an oil.

30 Dissolve the oil in 2B ethanol (312mL) and place in a 3L 3 neck round bottom flask equiped with an overhead stirrer, gas inlet and reflux condenser. Add anhydrous HCl (39g) and stir the mixture at 70C for 1 hour. Cool to 50C and add, by dropwise addition, aqueous 20% NaOH (641g), keeping
35 the temperature below 50C. After the addition, stir the mixture for an additional 1 hour at 50C, cool to room temperature and neutralize with acetic acid (6.25g).

Separate the layers and evaporate the solvent in vacuo to give the title compound (391g).

5

Example 16

Step h and step i: 2-(4-Cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, 2-ethylhexyl ester

- Mix methylene chloride (50mL), 2-ethylhexyl alcohol (130g, 1mol) and triethylamine (50g, 0.5mol). Add, by dropwise
10 addition, ethyl dimethylphenylacetyl chloride (91g, 0.5mol). Heat the reaction mixture to 68C for 1 hour, add methylene chloride (100mL) and stir overnight. Remove the solids by filtration, wash with methylene chloride (50mL), combine with the liquid organics, wash with aqueous 5% HCl,
15 (50mL), water (50mL) and dry over MgSO₄. Evaporate the solvent in vacuo and purify by distillation (119 C at 1mmHg) (105g, 76%).

- Place aluminum chloride (29.3g) and methylene chloride
20 (30mL) in a 250mL round bottom flask with an overhead stirrer, temperature control, condenser, additional funnel and nitrogen atmosphere. Add, by dropwise addition, chlorobutyl chloride (16.9g), keeping the temperature below 10C. After addition is complete, warm the reaction
25 mixture to 36C and hold for 24 hours. Quench the reaction mixture into ice/water (200g) and extract with methylene chloride (50mL). Wash the organics with water (50mL) and dry (MgSO₄). Evaporate the solvent in vacuo to give an oil (30g). Place the oil in a 250mL flask equipped with an
30 overhead stirrer, gas inlet, condenser and thermometer. Add 2B ethanol (150mL) followed by anhydrous HCl (5g). Heat the reaction mixture to 76C for 2.5 hours then add additional HCl (5g). Heat the reaction mixture at 76C for 22 hours, evaporate the solvent in vacuo to give an oil.
35 Dissolve the oil in 2B ethanol (100mL), treat with solid KOH (10g) and heat at reflux for 2 hours.

Example 17Step m and step l: 2-(4-Cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester

- 5 Dissolve 2-[4-(4-chloro-butyryl)-phenyl]-acetic acid, ethyl ester (28.5g) in toluene (50mL) and evaporate the solvent in *vacuo* to remove traces of ethanol. Dissolve the residue in diglyme (50mL) and add, by dropwise addition, to a suspension of sodium hydride (12.2g of a 60% suspension in
10 mineral oil) slurried in diglyme (150mL) containing methyl chloride (10g). Slowly add methyl chloride (10g) and stir for 15 minutes. Filter through filter aid, wash filtercake with acetonitrile and evaporate the solvent. Remove meta-isomer by distillation (150°C @ 1mm) and crystallize
15 (ethanol) to give the title compound (93%).

Example 18Step f and step : 2-(4-Cyclopropanecarbonyl-phenyl)-propionic acid, ethyl ester and 2-(3-Cyclopropanecarbonyl-phenyl)-propionic acid, ethyl ester

- 20 Dissolve 2-phenylpropionic acid (30g) in 2B ethanol (100mL) and add anhydrous HCl (10g). Allow to sit for 48-72 hours, evaporate the solvent in *vacuo* and purify by distillation to give ethyl 2-phenylpropionate (31g); bp 100C at 6mm.
25 Place aluminum chloride (49.4g, 0.371mole) and methylene chloride (50mL) in a 250mL 3-neck round bottom flask equipped with an overhead stirrer, addition funnel and thermometer. Cool to less than 10C and add, by dropwise
30 addition, chlorobutyrylchloride (23.8g, 0.202mol), keeping the temperature below 10C. After addition is complete, add, by dropwise addition, ethyl 2-phenylpropionate (30g, 0.17mol), keeping the temperature below 10C. Stir at room temperature for 1 hour then heat at reflux for 14 hours.
35 Quench into ice/water (350g) and filter through a celite pre-coat. Separate the layers and evaporate the solvent in *vacuo* to give a red oil.

Dissolve the red oil in 2B ethanol (35mL) and place in a round bottom flask with a condenser and gas inlet. Add anhydrous HCl (4.3g) and heat the solution to 70C for 1
5 hour. Cool the solution to 10C and add, by dropwise addition, 20% aqueous sodium hydroxide. Separate the layers and evaporate the solvent in vacuo to give an oil.

Re-treat the oil with HCl in 2B ethanol as above, cool to
10 10C and treat with a 20% solution of sodium ethoxide in ethanol. Neutralize with acetic acid, filter the solids and evaporate the solvent in vacuo. Purify by distillation to give the title compound; bp 161-167 at 1.2mm.

15

Example 19

Step h: 2-[4-(4-Chloro-butyryl)-phenyl]-2-methyl-propionic acid, ethyl ester and 2-[3-(4-Chloro-butyryl)-phenyl]-2-methyl-propionic acid, ethyl ester

Place AlCl₃ (146.5g, 1.1mol) and methylene chloride (75mL)
20 in a 3-neck, 500mL round-bottomed flask equipped with an overhead stirrer, bottom drop valve, thermometer, condenser and temperature control and cool to 15°C. Add, by dropwise addition, 4-chlorobutyryl chloride (84.5g, 0.6mol), keeping the temperature below 15°C. Add, by dropwise addition,
25 ethyl 2-methyl-2-phenylpropionate (96g, 0.5mol), keeping the temperature below 15° C. After addition is complete, stir the reaction mixture at 22°C for 1 hour, then heat at reflux (57°C) for 2 hours. Add the reaction mixture, by dropwise addition, by way of the bottom drop valve, to
30 water (500mL) at 95°C contained in a 2L 3 neck flask equipped with a magnetic stirbar, thermometer and distillation head. During addition, hold the reaction mixture at 70°C by allowing the methylene chloride to distill overhead. After the quench is complete, separate
35 the the organic layer, dry (MgSO₄) and evaporate the solvent in vacuo to give the title compound (150g).

The novel intermediates of formula (II), formula (III), formula (IV), formula (V), formula (VI) and formula (VII) wherein R_5 is CONR_6R_7 may also be prepared as described in Scheme G. In Scheme G, all substituents are as previously defined unless otherwise indicated.

Scheme G

10

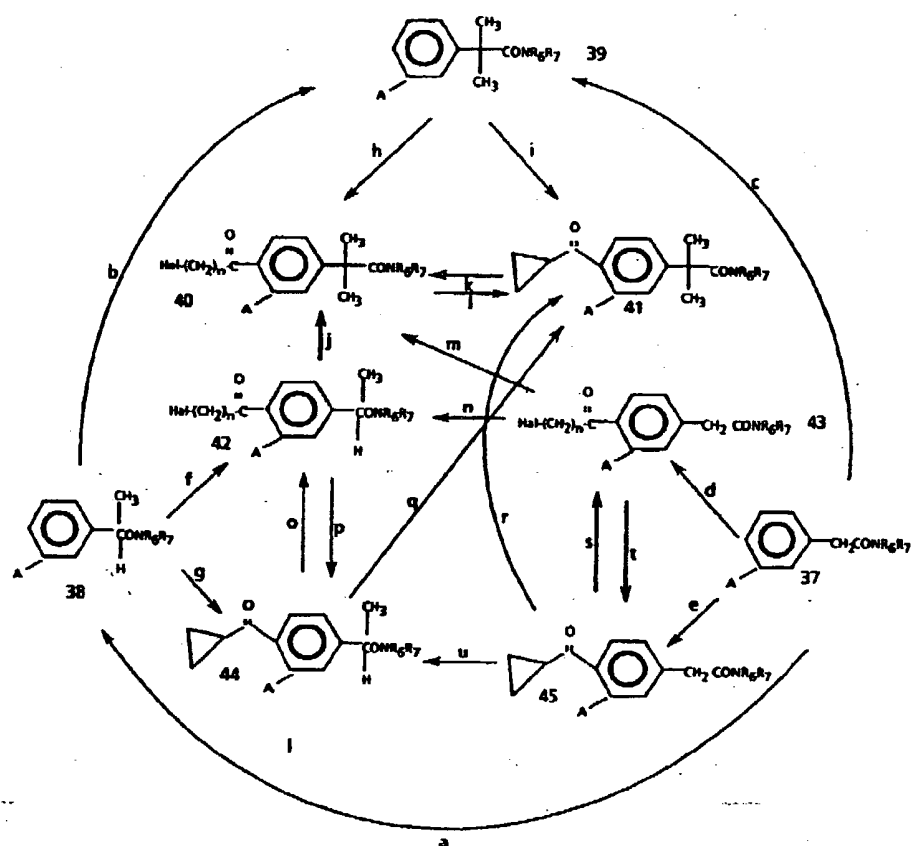
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Scheme G provides alternative various general synthetic procedures for preparing the novel intermediates of formula (II), formula (III), formula (IV), formula (V), formula (VI) and formula (VII) wherein R_5 is $CONR_6R_7$.

In step a, the appropriate phenylacetic acid amide compound of structure (37) is methylated to give the corresponding α -methylphenylacetic acid amide compound of structure (38) as described previously in Scheme A, step a.

Appropriate phenylacetic acid amide compound of structure (37) are prepared from the corresponding phenylacetic acid by standard amide-forming reactions as are known in the art. The appropriate phenylacetic acids may be prepared by hydrolisis of the corresponding 2-cyano-2-propylbenzene compound of structure (27) by techniques and procedures well known and appreciated by one of ordinary skill in the art.

20

In step b, the appropriate α -methylphenylacetic acid amide compound of structure (38) is methylated to give the corresponding α,α -dimethylphenylacetic acid amide compound of structure (39) as described previously in Scheme A, step a.

25

Appropriate α -methylphenylacetic acid amide compound of structure (38) are prepared from the corresponding α -methylphenylacetic acid by standard amide-forming reactions as are known in the art as as described in step a.

30

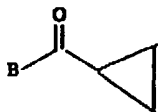
In step c, the appropriate phenylacetic acid amide compound of structure (37) is dimethylated to give the corresponding α,α -dimethylphenylacetic acid amide compound of structure (39) as described previously in Scheme A, step c.

35

In step d, the appropriate phenylacetic acid amide compound of structure (37) is acylated with an appropriate ω -halo compound of the structure $\text{Hal}-(\text{CH}_2)_n-\text{C}(=\text{O})-\text{B}$, wherein B is Hal or hydroxy, Hal is Cl, Br or I and n is as previously defined to give the corresponding ω' -halo- α' -keto-phenylacetic acid amide compound of structure (43) as described previously in Scheme A, step d.

10 In step e, the appropriate phenylacetic acid amide compound of structure (37) is acylated with an appropriate cyclopropyl compound of the structure

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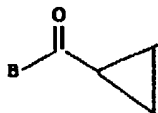
wherein B is as previously defined to give the corresponding cyclopropylketo-phenylacetic acid amide compound of structure (45) as described previously in Scheme A, step e.

25 In step f, the appropriate α -methylphenylacetic acid amide compound of structure (38) is acylated with an appropriate ω -halo compound of the structure $\text{Hal}-(\text{CH}_2)_n-\text{C}(=\text{O})-\text{B}$, wherein B is Hal or hydroxy, Hal is Cl, Br or I and n is as previously defined to give the corresponding ω' -halo- α' -keto- α -methylphenylacetic acid amide compound of structure (42) as described previously in Scheme A, step d.

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In step g, the appropriate α -methylphenylacetic acid amide compound of structure (38) is acylated with an appropriate cyclopropyl compound of the structure

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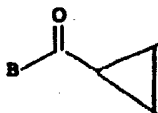


wherein B is as previously defined to give the corresponding cyclopropylketo- α -methylphenylacetic acid amide compound of structure (44) as described previously in Scheme A, step e.

In step h, the appropriate α,α -dimethylphenylacetic acid amide compound of structure (39) is acylated with an appropriate ω -halo compound of the structure $\text{Hal}-(\text{CH}_2)_n-\text{C}(=\text{O})-\text{B}$, wherein B is Hal or hydroxy, Hal is Cl, Br or I and n is as previously defined to give the corresponding ω' -halo- α' -keto- α,α -di-methylphenylacetic acid amide compound of structure (40) as described previously in Scheme A, step d.

Appropriate α,α -dimethylphenylacetic acid amide compound of structure (39) are prepared from the corresponding α,α -dimethylphenylacetic acid by standard amide-forming reactions as are known in the art as as described in step a.

In step i, the appropriate α,α -dimethylphenylacetic acid amide compound of structure (39) is acylated with an appropriate cyclopropyl compound of the structure



wherein B is as previously defined to give the corresponding cyclopropylketo- α,α -dimethylphenylacetic acid amide compound of structure (41) as described previously in Scheme A, step e.

In step j, the appropriate ω' -halo- α' -keto- α,α -methylphenylacetic acid amide compound of structure (42) is methylated to give the corresponding ω' -halo- α' -keto- α,α -

di-methylphenylacetic acid amide compound of structure (40) as described previously in Scheme a, step a.

- 5 In step k, the cyclopropyl functionality of the appropriate cyclopropylketo- α,α -dimethylphenylacetic acid amide compound of structure (41) is ring-opened to give the corresponding ω' -halo- α' -keto- α,α -di-methylphenylacetic acid amide compound of structure (40) wherein $n = 3$ as
10 described previously in Scheme A, step j.

- In step l, the appropriate ω' -halo- α' -keto- α,α -di-methylphenylacetic acid amide compound of structure (40) wherein $n = 3$ is ring-closed to give the corresponding
15 cyclopropylketo- α,α -dimethylphenylacetic acid amide compound of structure (41) as described previously in Scheme A, step k.

- In step m, the appropriate ω' -halo- α' -keto-phenylacetic
20 acid amide compound of structure (43) is dimethylated to give the corresponding ω' -halo- α' -keto- α,α -di-methylphenylacetic acid amide compound of structure (40) as described previously in Scheme A, step c.

- 25 In step n, the appropriate ω' -halo- α' -keto-phenylacetic acid amide compound of structure (43) is methylated to give the corresponding ω' -halo- α' -keto- α -methylphenylacetic acid amide compound of structure (42) as described previously in Scheme A, step a.

- 30 In step o, the cyclopropyl functionality of the appropriate cyclopropylketo- α -methylphenylacetic acid amide compound of structure (44) is ring-opened to give the corresponding ω' -halo- α' -keto- α -methylphenylacetic acid
35 amide compound of structure (42) wherein $n = 3$ as described previously in Scheme A, step j.

In step p, the appropriate ω' -halo- α' -keto- α -methylphenylacetic acid amide compound of structure (42) wherein $n = 3$ is ring-closed to give the corresponding
5 cyclopropylketo- α -methylphenylacetic acid amide compound of structure (44) as described previously in Scheme A, step k.

In step q, the appropriate cyclopropylketo- α -methylphenylacetic acid amide compound of structure (44) is
10 methylated to give the corresponding cyclopropylketo- α,α -dimethylphenylacetic acid amide compound of structure (41) as described previously in Scheme A, step a.

In step r, the appropriate cyclopropylketo-phenylacetic
15 acid amide compound of structure (45) is dimethylated to give the corresponding cyclopropylketo- α,α -dimethylphenylacetic acid amide compound of structure (41) as described previously in Scheme A, step c.

20 In step s, the cyclopropyl functionality of the appropriate cyclopropylketo-phenylacetic acid amide compound of structure (45) is ring-opened to give the corresponding ω' -halo- α' -keto-phenylacetic acid amide compound of structure (43) wherein $n = 3$ as described
25 previously in Scheme A, step j.

In step t, the appropriate ω' -halo- α' -keto-phenylacetic acid amide compound of structure (43) wherein $n = 3$ is ring-closed to give the corresponding cyclopropylketo-
30 phenylacetic acid amide compound of structure (45) as described previously in Scheme A, step k.

In step u, the appropriate cyclopropylketo-phenylacetic acid amide compound of structure (45) is methylated to give
35 the corresponding cyclopropylketo- α -methylphenylacetic acid amide compound of structure (44) as described previously in Scheme A, step a.

Starting materials for use in Scheme G are readily available to one of ordinary skill in the art.

- 5 The following examples present typical syntheses as described in Scheme G. These examples are understood to be illustrative only and are not intended to limit the scope of the present invention in any way. As used herein, the following terms have the indicated meanings: "g" refers to
10 grams; "mmol" refers to millimoles; "mL" refers to milliliters; "bp" refers to boiling point; "°C" refers to degrees Celsius; "mm Hg" refers to millimeters of mercury; "μL" refers to microliters; "μg" refers to micrograms; and "μM" refers to micromolar.

15

Example 20

Step h: 2-[4-(4-Chloro-butyryl)-phenyl]-2-methyl-propionic acid, N-methoxy-N-methylamide

- Dissolve 2-methyl-2-phenyl-propionic acid (15.0g, 91.2mmol)
20 in toluene (80mL) and add, by dropwise addition over 5 minutes, thionyl chloride (15mL, 206mmol). Stir at room temperature overnight, add additional thionyl chloride (3mL, 41.1mmol) and heat to reflux for 1 hour. Remove excess thionyl chloride by azeotropic distillation with
25 toluene (40mL). Add toluene (20mL) to the reaction mixture along with a solution of potassium carbonate (28.0g, 203mmol) in water (40mL). Add, by dropwise addition, a solution of N,O-dimethylhydroxylamine hydrochloride (8.9g, 91.2mmol) in water (20mL) without cooling and stir for 2
30 hours. Add tert-butylmethyl ether (75mL) following by slow addition of aqueous HCl (2N, 75mL) with vigorous stirring. Separate the organic layer and wash with aqueous HCl (2N, 75mL), saturated sodium hydrogen carbonate (25mL) and brine (50mL). Dry the organic layer over (Na₂SO₄), filter,
35 evaporate the filtrate *in vacuo* and purify by vacuum distillation to give 2-methyl-2-phenyl-propionic acid, N-methoxy-N-methylamide (18.0g, 95%); bp 91-103°C/5mm Hg.

MS (CI, CH₄) m/e 208 (M⁺+1, 100), 119.

- Slurry AlCl₃ (10.15g, 76.1mmol) and methylene chloride
5 (45mL) under a nitrogen atmosphere at room temperature.
Add 4-chlorobutyryl chloride (4.27mL, 38.1mmol), stir for
20 minutes and add, by dropwise addition over 10 minutes, a
solution of 2-methyl-2-phenyl-propionic acid, N-methoxy-N-
methylethylamide (6.58g, 31.7mmol) in methylene chloride (15mL).
10 Stir at room temperature for 45 minutes, then heat at 30-
35°C for 7 hours. Pour into ice water (150mL) and separate
the layers. Wash the aqueous layer with water (3X75mL),
combine the aqueous layers and extract with methylene
chloride (2X75mL). Combine the organic layers and dry
15 (Na₂SO₄). Filter, evaporate the filtrate *in vacuo* and purify
by silica gel chromatography (3:1 hexane/ethyl acetate) to
give the title compound (6.19g, 63%) as a light yellow oil.

MS (CI, CH₄) m/e 312 (M⁺+1), 276.

20

Example 21

Step h: 2-[4-(4-Chloro-butyryl)-phenyl]-2-methyl-propionic acid, dimethylamide

- Dissolve 2-methyl-2-phenyl-propionic acid (15.0g, 91.2mmol)
25 in toluene (80mL) and add, by dropwise addition over 5
minutes, thionyl chloride (15mL, 206mmol). Stir at room
temperature overnight, add additional thionyl chloride
(3mL, 41.1mmol) and heat to reflux for 1 hour. Remove
excess thionyl chloride by azeotropic distillation with
30 toluene (40mL). Add toluene (20mL) to the reaction mixture
along with a solution of potassium carbonate (28.0g,
203mmol) in water (40mL). Add, by dropwise addition, a 40%
aqueous solution of dimethylamine hydrochloride (20mL,
0.18mol) without cooling and stir for 2 hours. Add tert-
35 butylmethyl ether (75mL) following by slow addition of
aqueous HCl (2N, 75mL) with vigorous stirring. Separate
the organic layer and wash with aqueous HCl (2N, 75mL),
saturated sodium hydrogen carbonate (25mL) and brine

- (50mL). Dry the organic layer over (Na_2SO_4), filter, evaporate the filtrate *in vacuo* and purify by crystallization to give 2-methyl-2-phenyl-propionic acid, dimethylamide
- 5 (15.35g, 88%) as a white solid; mp 57-59°C.

Anal. Calcd for $\text{C}_{12}\text{H}_{17}\text{NO}$: C, 75.35; H, 8.96; N, 7.32;
Found: C, 75.12; H, 8.86; N, 7.26.

- 10 Add AlCl_3 (1.12g, 8.40mmol) to carbon tetrachloride (6mL) under a nitrogen atmosphere at room temperature. Add 4-chlorobutyl chloride (0.49mL, 4.37mmol), stir for 15 minutes and add, by dropwise addition over 3 minutes, a solution of 2-methyl-2-phenyl-propionic acid, dimethylamide
- 15 (0.64g, 3.36mmol) in carbon tetrachloride (6mL). Stir at room temperature for 17 hours, dilute with methylene chloride (10mL), pour into ice water (50mL) and separate the layers. Wash the aqueous layer with methylene chloride (2X70mL), 5% aqueous sodium hydrogen carbonate, combine the
- 20 organic layers and dry (Na_2SO_4). Filter, evaporate the filtrate *in vacuo* and purify by silica gel chromatography (5:2 hexane/ethyl acetate) to give the title compound (0.72g, 72%) as a light yellow oil.

25 Example 22

Step h: 2-[4-(4-Chloro-butyl)-phenyl]-2-methyl-propionic acid, pyrrolidineamide

- Dissolve 2-methyl-2-phenyl-propionic acid (15.0g, 91.2mmol) in toluene (80mL) and add, by dropwise addition over 5
- 30 minutes, thionyl chloride (15mL, 206mmol). Stir at room temperature overnight, add additional thionyl chloride (3mL, 41.1mmol) and heat to reflux for 1 hour. Remove excess thionyl chloride by azeotropic distillation with toluene (40mL). Add toluene (20mL) to the reaction mixture
- 35 along with a solution of potassium carbonate (28.0g, 203mmol) in water (40mL). Add, by dropwise addition, pyrrolidine (7.61mL, 91mmol) without cooling and stir for 2 hours. Add tert-butylmethyl ether (75mL) following by slow

addition of aqueous HCl (2N, 75mL) with vigorous stirring. Separate the organic layer and wash with aqueous HCl (2N, 75mL), saturated sodium hydrogen carbonate (25mL) and brine
5 (50mL). Dry the organic layer over (Na₂SO₄), filter, evaporate the filtrate *in vacuo* and purify by crystallization to give 2-methyl-2-phenyl-propionic acid, pyrrolidineamide (18.28g, 92%) as a solid; mp 96-97°C.

10 Anal. Calcd for C₁₄H₁₉NO: C, 77.38; H, 8.81; N, 6.45;
Found: C, 77.21; H, 8.70; N, 6.41.

Add AlCl₃ (8.31g, 62.3mmol) to carbon tetrachloride (65mL) under a nitrogen atmosphere at room temperature. Add 4-
15 chlorobutyl chloride (03.5mL, 31.2mmol), stir for 15 minutes and add, by dropwise addition over 15 minutes, a solution of 2-methyl-2-phenyl-propionic acid, pyrrolidineamide (5.64g, 26.0mmol) in carbon tetrachloride (60mL). Stir at room temperature for 17 hours, pour into
20 ice water (100mL) and separate the layers. Wash the aqueous layer with methylene chloride (2X70mL), 5% aqueous sodium hydrogen carbonate, combine the organic layers and dry (Na₂SO₄). Filter, evaporate the filtrate *in vacuo* and purify by silica gel chromatography (5:2 hexane/ethyl
25 acetate) to give the title compound (6.55g, 78%) as a light yellow oil.

Example 23

Step 1: 2-(4-Cyclopropanecarbonyl-phenyl)-2-methyl-
30 propionic acid, N-methoxy-N-methylamide
Add potassium hydroxide (13g) to 2-[4-(4-chloro-butyl-phenyl)-2-methyl-propionamide, N-methoxy-N-methylamide (96.6mmol) and stir at room temperature for 40 minutes, filter and wash the filtercake with ethanol. Evaporate the
35 ethanol in vacuo, dissolve in methylene chloride (100mL), wash with water (50mL), 5% sodium hydrogen carbonate (50mL) and water (50mL). Evaporate the solvent in vacuo, removing water with toluene azeotrope. Purify the product by

distillation followed by recrystallization (heptane) to give the title compound (7.4g).

- 5 The following compounds can be prepared by procedures depicted in Scheme G:

(4-cyclopropanecarbonyl-phenyl)-acetic acid, N-methoxy-N-methylamide;

10

(4-cyclopropanecarbonyl-phenyl)-acetic acid, dimethylamide;

(4-cyclopropanecarbonyl-phenyl)-acetic acid, pyrrolidineamide;

15

2-(4-Cyclopropanecarbonyl-phenyl)-propionic acid, N-methoxy-N-methylamide;

20 2-(4-Cyclopropanecarbonyl-phenyl)-propionic acid, dimethylamide;

2-(4-Cyclopropanecarbonyl-phenyl)-propionic acid, pyrrolidineamide;

25 2-(4-Cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, N-methoxy-N-methylamide;

2-(4-Cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, dimethylamide;

30

2-(4-Cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, pyrrolidineamide;

35 [4-(4-Chloro-butyryl)-phenyl]-acetic acid, N-methoxy-N-methylamide;

[4-(4-Chloro-butyryl)-phenyl]-acetic acid, dimethylamide;

[4-(4-Chloro-butyryl)-phenyl]-acetic acid, pyrroldineamide;

2-[4-(4-Chloro-butyryl)-phenyl]-propionic acid, N-methoxy-
5 N-methylamide;

2-[4-(4-Chloro-butyryl)-phenyl]-propionic acid,
dimethylamide;

10 2-[4-(4-Chloro-butyryl)-phenyl]-propionic acid,
pyrroldineamide;

2-[4-(4-Chloro-butyryl)-phenyl]-2-methyl-propionic acid, N-
methoxy-N-methylamide;

15

2-[4-(4-Chloro-butyryl)-phenyl]-2-methyl-propionic acid,
dimethylamide;

2-[4-(4-Chloro-butyryl)-phenyl]-2-methyl-propionic acid,
20 pyrroldineamide;

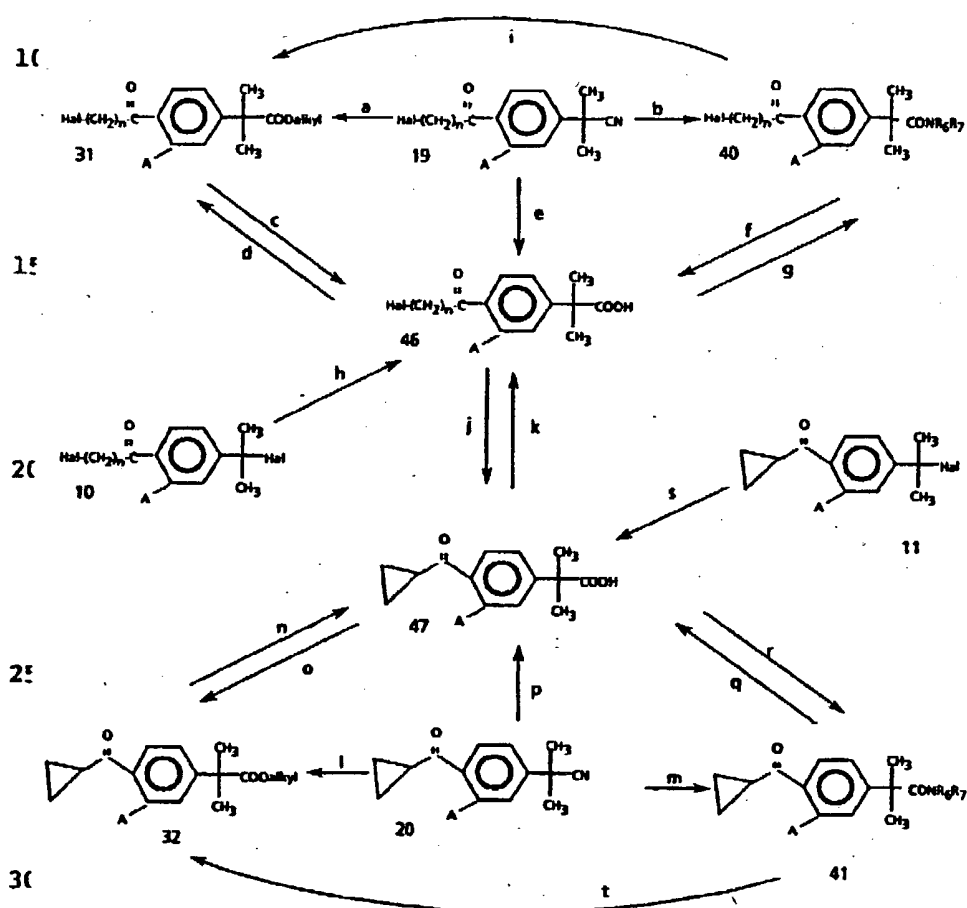
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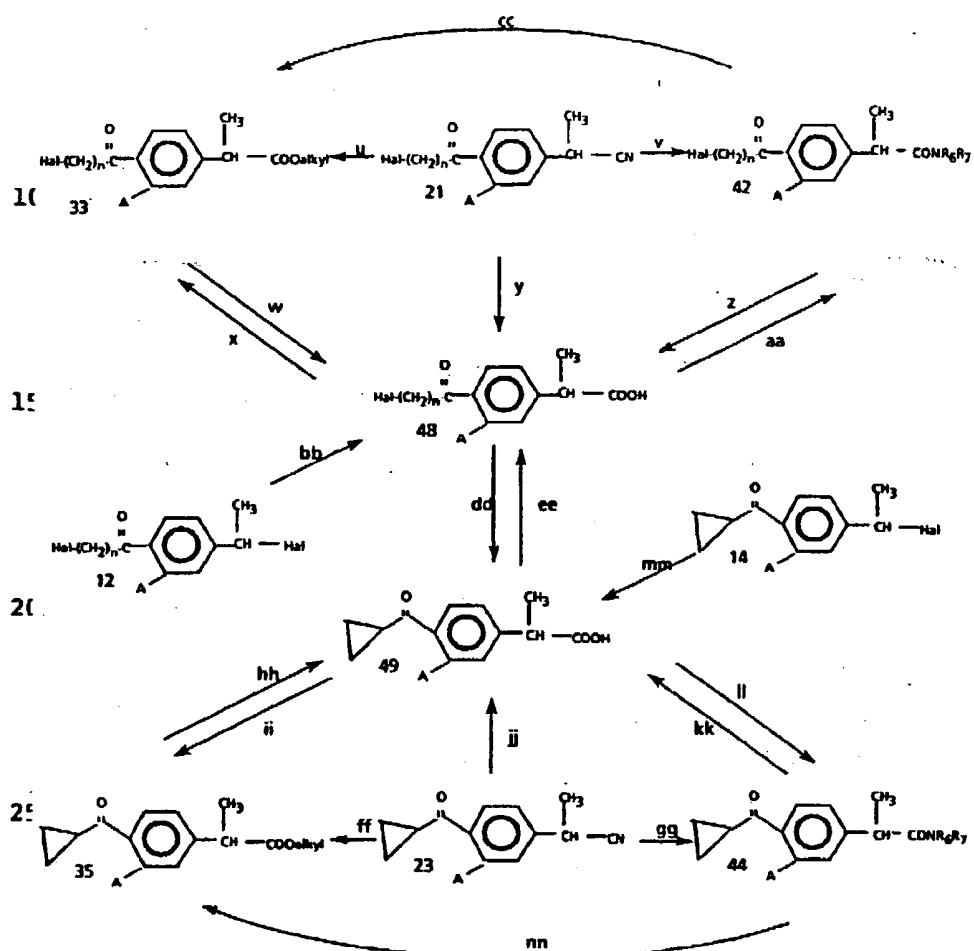
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The novel intermediates of formula (II), formula (III), formula (IV), formula (V), formula (VI) and formula (VII) wherein R_5 is COOH, COOalkyl or CONR₆R₇ may be prepared as described in Scheme H. In Scheme H, all substituents are as previously defined unless otherwise indicated.

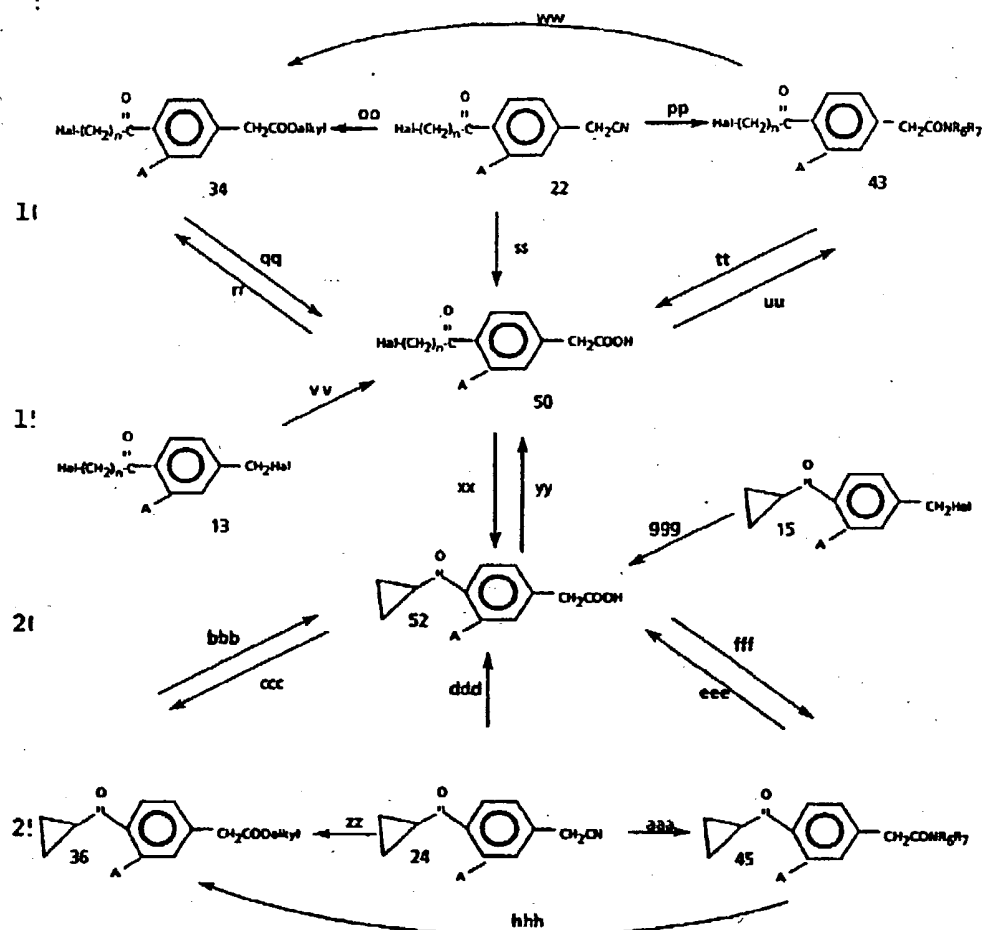
Scheme H



Scheme H Cont.



Scheme H Cont.



31

Scheme H provides various general synthetic procedures for preparing the novel intermediates of formula (II), formula (III), formula (IV), formula (V), formula (VI) and formula (VII) wherein R₅ is COOH, COOalkyl or CONR₆R₇.

In step a, the nitrile functionality of the appropriate ω-halo-cyanocumylketone compound of structure (19) is

converted to the corresponding ester by reaction with an appropriate C₁ to C₆ alcohol to give the corresponding ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound of structure (31).

For example, the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound of structure (31) may be prepared by reacting an appropriate ω -halo-cyanocumylketone compound of structure (19) with an appropriate C₁-C₆ alcohol in the presence of a suitable anhydrous acid followed by treatment with water. Examples of appropriate alcohols are methanol, ethanol, propanol, and the like, with methanol being preferred. Examples of appropriate acids are hydrogen chloride and hydrogen bromide, with hydrogen chloride being preferred. The reaction time varies from about 1/2 hour to 48 hours, preferably 3 to 5 hours and the reaction temperature varies from about -20°C to room temperature, preferably -10°C to 0°C. The ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound of structure (28) is recovered from the reaction zone by evaporation of the solvent followed by extraction as is known in the art. The ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound of structure (31) may be purified by procedures well known in the art, such as chromatography.

In step b, the nitrile functionality of the appropriate ω -halo-cyanocumylketone compound of structure (19) is converted to the corresponding amide to give the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid amide compound of structure (40) wherein R₆ and R₇ are both hydrogen.

For example, hydrolysis may be achieved by using a suitable acid, such as concentrated hydrochloric acid as is known in the art.

In step c, the carboxy ester functionality of the appropriate ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound of structure (31) is hydrolyzed to give the
5 corresponding ω' -halo- α' -keto- α,α -dimethylphenylacetic acid compound of structure (46).

For example, hydrolysis may be achieved by using a suitable non-nucleophilic base, such as sodium methoxide in
10 methanol as is known in the art. Other methods known in the art for ester cleavage include potassium carbonate in methanol, methanolic ammonia, potassium carbonate, potassium hydroxide, calcium hydroxide, sodium hydroxide, magnesium hydroxide, sodium hydroxide/pyridine in methanol,
15 potassium cyanide in ethanol and sodium hydroxide in aqueous alcohols, with potassium hydroxide being preferred. The reaction is typically carried out in an aqueous lower alcohol solvent, such as methanol, ethanol, isopropyl alcohol, n-butanol, 2-ethoxyethanol or ethylene glycol or
20 pyridine, at temperatures ranging from room temperature to the reflux temperature of the solvent, and the reaction time varies from about 1/2 hour to 100 hours.

In step d, the carboxy functionality of the appropriate
25 ω' -halo- α' -keto- α,α -dimethylphenylacetic acid compound of structure (46) may be esterified by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound of structure
30 (31).

For example, one such method involves reacting an appropriate ω' -halo- α' -keto- α,α -dimethylphenylacetic acid compound of structure (46) with an excess of an appropriate
35 C₁-C₆ alcohol which is straight or branched in the presence of a small amount of mineral acid, such as hydrochloric acid or sulfuric acid, hydrochloric acid being preferred, at reflux. Another suitable method involves reacting an

appropriate ω' -halo- α' -keto- α,α -dimethylphenylacetic acid compound of structure (46) with an excess of diazomethane in a suitable solvent such as ether at room temperature to give the methyl ester. In addition, the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound of structure (28) may also be prepared by reacting an appropriate ω' -halo- α' -keto- α,α -di-methylphenylacetic acid compound of structure (46) with an excess of 2,2-dimethoxypropane in a suitable solvent such as methanol at 0°C to room temperature to give the methyl ester. Another suitable method involves first reacting an appropriate ω' -halo- α' -keto- α,α -dimethylphenylacetic acid compound of structure (46) with thionyl chloride in a suitable solvent such as methylene chloride to give an intermediate acid chloride, followed by addition of a suitable C₁ to C₆ alcohol which is straight or branched. Another suitable method involves the alkylation of the carboxylate anion with an appropriate electrophile, such as dimethyl sulfate or ethyl bromide, to give the corresponding ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound of structure (31). Such methods are well known in the art and are described in *J. Org. Chem.*, 29, 2490-2491 (1964).

Alternatively, step k and step d may be combined and the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound of structure (34) wherein n = 3 may be prepared from the corresponding cyclopropylketo- α,α -dimethylphenylacetic acid compound of structure (50).

Alternatively, step p, step k and step d may be combined and the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound of structure (31) wherein n = 3 may be prepared from the corresponding cyclopropyl cyanocumylketone compound of structure (20).

In step e, the nitrile functionality of the appropriate ω -halo-cyanocumylketone compound of structure (19) is converted to the corresponding carboxy to give the ω' -halo-

α' -keto- α,α -dimethylphenylacetic acid compound of structure (46).

- 5 For example, hydrolysis may be achieved by using a suitable acid, such as concentrated hydrochloric acid as is known in the art.

10 In step f, the amide functionality of the appropriate ω' -halo- α' -keto- α,α -dimethylphenylacetic acid amide compound of structure (40) is converted to the corresponding acid by acid hydrolysis as is known in the art to give the corresponding ω' -halo- α' -keto- α,α -dimethylphenylacetic acid compound of structure (46).

15

- For example, hydrolysis may be achieved by using a suitable non-nucleophilic base, such as sodium methoxide in methanol as is known in the art. Other methods known in the art for ester cleavage include potassium carbonate in
20 methanol, methanolic ammonia, potassium carbonate, potassium hydroxide, calcium hydroxide, sodium hydroxide, magnesium hydroxide, sodium hydroxide/pyridine in methanol, potassium cyanide in ethanol and sodium hydroxide in aqueous alcohols, with potassium hydroxide being preferred. The
25 reaction is typically carried out in an aqueous lower alcohol solvent, such as methanol, ethanol, isopropyl alcohol, n-butanol, 2-ethoxyethanol or ethylene glycol or pyridine, at temperatures ranging from room temperature to the reflux temperature of the solvent, and the reaction
30 time varies from about 1/2 hour to 100 hours.

- In step g, the carboxy functionality of the appropriate ω' -halo- α' -keto- α,α -dimethylphenylacetic acid compound of structure (46) may be amidated by techniques and procedures
35 well known and appreciated by one of ordinary skill in the art to give the corresponding ω' -halo- α' -keto- α,α -dimethylphenylacetic acid amide compound of structure (40).

In step h, the α -halo functionality of the appropriate ω -halo-halocumylketone compound of structure (10) is carboxylated to give the corresponding ω' -halo- α' -keto- α,α -dimethylphenylacetic acid compound of structure (46).

For example, a solution of the appropriate ω -halo-halocumylketone compound of structure (10) and a suitable catalyst, such as tetraethylammonium bromide, in a suitable polar aprotic organic solvent, such as acetonitrile, N,N-dimethylacetamide, 1-methyl-2-pyrrolidinone or dimethylformamide, are placed in a jacketed glass cell and fitted with an expanded silver mesh cathode, magnesium anode and carbon dioxide delivery tube. Rotation of the electrodes provides stirring, while electrical contact with the electrodes is made via spring loaded sliding carbon brushes placed against the concentric metal shafts (insulated from each other with a length of plastic tubing) onto which the electrodes are mounted. Carbon dioxide is introduced into the cell at pressures of 1-10 atm, for a period of time ranging from 30 minutes to 50 hours and at a temperature range of from -30°C to 50°C. The corresponding ω' -halo- α' -keto- α,α -dimethylphenylacetic acid compound of structure (46) is isolated, after acidification with a suitable mineral acid, such as hydrochloric acid, by extractive methods as are known in the art.

It is preferred that the ω -halo functionality of the appropriate ω -halo-halocumylketone compound of structure (10) for use in step h be a ω -chloro.

Alternatively, the treatment of appropriate ω -halo-halocumylketone compound of structure (10) with a transition metal catalyst such as palladium, nickel or cobalt, optionally in the presence of a phosphine catalysis using low to modest pressures of carbon monoxide as described by Stahly et al. in U.S. Patent 4,990,658, 1991

also provides the corresponding ω' -halo- α' -keto- α,α -dimethylphenylacetic acid compound of structure (46).

5 In step i, the appropriate the amide functionality of the appropriate ω' -halo- α' -keto- α,α -dimethylphenylacetic acid amide compound of structure (40) is converted to the corresponding ester to give the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound of structure (31).

10

For example, the appropriate ω' -halo- α' -keto- α,α -dimethylphenylacetic acid amide compound of structure (40) is reacted with an appropriate hydrogen halide in an appropriate organic solvent such as ethanol. The reaction
15 is typically conducted at a temperature range of from room temperature to reflux and for a period of time ranging from 5 minutes to 1 hour. The ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound of structure (31) is recovered from the reaction zone by extractive methods
20 as is known in the art.

In step j, the appropriate ω' -halo- α' -keto- α,α -dimethylphenylacetic acid compound of structure (46)
wherein $n = 3$ is ring-closed to give the corresponding
25 cyclopropylketo- α,α -dimethylphenylacetic acid compound of structure (47) as described previously in Scheme A, step k.

In step k, the appropriate cyclopropylketo- α,α -dimethylphenylacetic acid compound of structure (47) is
30 ring-opened to give the corresponding ω' -halo- α' -keto- α,α -dimethylphenylacetic acid compound of structure (46) wherein $n = 3$ as described previously in Scheme A, step j.

In step l, the nitrile functionality of the appropriate
35 cyclopropyl cyanocumylketone compound of structure (20) is converted to the corresponding ester by reaction with an appropriate C_1 to C_6 alcohol to give the cyclopropylketo-

-111-

α,α -dimethylphenylacetic acid ester compound of structure (32) as described previously in step a.

5 In step m, the nitrile functionality of the appropriate cyclopropyl cyanocumylketone compound of structure (20) is converted to the corresponding amide to give the ω' -halo- α' -keto- α,α -di-methylphenylacetic acid amide compound of structure (41) wherein R_6 and R_7 are both hydrogen as
10 described previously in step b.

In step n, the carboxy ester functionality of the appropriate cyclopropylketo- α,α -dimethylphenylacetic acid ester compound of structure (32) is hydrolyzed to give the
15 corresponding cyclopropylketo- α,α -dimethylphenylacetic acid compound of structure (47) as described previously in step c.

In step o, the carboxy functionality of the appropriate
20 cyclopropylketo- α,α -dimethylphenylacetic acid compound of structure (47) may be esterified by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding cyclopropylketo- α,α -dimethylphenylacetic acid ester compound of structure
25 (32) as described previously in step d.

In step p, the nitrile functionality of the appropriate cyclopropyl cyanocumylketone compound of structure (20) is converted to the corresponding carboxy to give the
30 cyclopropylketo- α,α -dimethylphenylacetic acid compound of structure (47) as described previously in step e.

In step q, the amide functionality of the appropriate cyclopropylketo- α,α -dimethylphenylacetic acid amide
35 compound of structure (41) is converted to the corresponding acid by acid hydrolysis as is known in the art to give the corresponding cyclopropylketo- α,α -

dimethylphenylacetic acid compound of structure (47) as described previously in step f.

- 5 In addition, step q and step k may be combined and the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid compound of structure (46) wherein $n = 3$ may be prepared from the corresponding cyclopropylketo- α,α -dimethylphenylacetic acid amide compound of structure (41) as described previously in
10 Scheme A, step j.

- In step r, the carboxy functionality of the appropriate cyclopropylketo- α,α -dimethylphenylacetic acid compound of structure (47) may be amidated by techniques and procedures
15 well known and appreciated by one of ordinary skill in the art to give the corresponding cyclopropylketo- α,α -dimethylphenylacetic acid amide compound of structure (41) as described previously in step g.

- 20 In step s, the α -halo functionality of the appropriate cyclopropyl halocumylketone compound of structure (11) is carboxylated to give the corresponding cyclopropylketo- α,α -dimethylphenylacetic acid compound of structure (47) as described previously in step h.

- 25 In step t, the appropriate the amide functionality of the appropriate cyclopropylketo- α,α -dimethylphenylacetic acid amide compound of structure (41) is converted to the corresponding ester to give the cyclopropylketo- α,α -
30 dimethylphenylacetic acid ester compound of structure (32) as described previously in step i.

- In step u, the nitrile functionality of the appropriate ω -halo-cyanoethylphenylketone compound of structure (21) is
35 converted to the corresponding ester by reaction with an appropriate C_1 to C_6 alcohol to give the ω' -halo- α' -keto- α -methylphenylacetic acid ester compound of structure (33) as described previously in step a.

In step v, the nitrile functionality of the appropriate ω -halo-cyanoethylphenylketone compound of structure (21) is converted to the corresponding amide to give the ω' -halo- α' -keto- α -methylphenylacetic acid amide compound of structure (42) wherein R_6 and R_7 are both hydrogen as described previously in step b.

In step w, the carboxy ester functionality of the appropriate ω' -halo- α' -keto- α -methylphenylacetic acid ester compound of structure (33) is hydrolyzed to give the corresponding ω' -halo- α' -keto- α -methylphenylacetic acid compound of structure (48) as described previously in step c.

15

In step x, the carboxy functionality of the appropriate ω' -halo- α' -keto- α -methylphenylacetic acid compound of structure (48) may be esterified by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding ω' -halo- α' -keto- α -methylphenylacetic acid ester compound of structure (33) as described previously in step d.

Alternatively, step ee and step x may be combined and the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound of structure (33) wherein $n = 3$ may be prepared from the corresponding cyclopropylketo- α -methylphenylacetic acid compound of structure (49) as described previously in step d.

30

Alternatively, step jj, step ee and step x may be combined and the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound of structure (33) wherein $n = 3$ may be prepared from the corresponding cyclopropyl cyanoethylphenylketone compound of structure (23) as described previously in step d.

35

In step y, the nitrile functionality of the appropriate ω -halo-cyanoethylphenylketone compound of structure (21) is converted to the corresponding carboxy to give the ω' -halo- α' -keto- α -methylphenylacetic acid compound of structure (48) as described previously in step e.

In step z, the amide functionality of the appropriate ω' -halo- α' -keto- α -methylphenylacetic acid amide compound of structure (42) is converted to the corresponding acid by acid hydrolysis as is known in the art to give the ω' -halo- α' -keto- α -methylphenylacetic acid compound of structure (48) as described previously in step f.

In step aa, the carboxy functionality of the appropriate ω' -halo- α' -keto- α -methylphenylacetic acid compound of structure (48) may be amidated by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding ω' -halo- α' -keto- α -methylphenylacetic acid amide compound of structure (42) as described previously in step g.

In step bb, the α -halo functionality of the appropriate ω -halo-haloethylphenylketone compound of structure (12) is carboxylated to give the corresponding ω' -halo- α' -keto- α -methylphenylacetic acid compound of structure (48) as described previously in step h.

In step cc, the appropriate the amide functionality of the appropriate ω' -halo- α' -keto- α -methylphenylacetic acid amide compound of structure (42) is converted to the corresponding ester to give the ω' -halo- α' -keto- α -methylphenylacetic acid ester compound of structure (33) as described previously in step i.

In step dd, the appropriate ω' -halo- α' -keto- α -methylphenylacetic acid compound of structure (48) wherein $n = 3$ is ring-closed to give the corresponding

cyclopropylketo- α -methylphenylacetic acid compound of structure (49) as described previously in Scheme A, step k.

5 In step ee, the appropriate cyclopropylketo- α -methylphenylacetic acid compound of structure (49) is ring-opened to give the corresponding ω' -halo- α' -keto- α -methylphenylacetic acid compound of structure (48) wherein $n = 3$ as described previously in Scheme A, step j.

10

In step ff, the nitrile functionality of the appropriate cyclopropyl cyanoethylphenylketone compound of structure (23) is converted to the corresponding ester by reaction with an appropriate C_1 to C_6 alcohol to give the
15 cyclopropylketo- α -methylphenylacetic acid ester compound of structure (35) as described previously in step a.

In step gg, the nitrile functionality of the appropriate cyclopropyl cyanoethylphenylketone compound of
20 structure (23) is converted to the corresponding amide to give the cyclopropylketo- α -methylphenylacetic acid amide compound of structure (44) wherein R_6 and R_7 are both hydrogen as described previously in step b.

25 In step hh, the carboxy ester functionality of the appropriate cyclopropylketo- α -methylphenylacetic acid ester compound of structure (35) is hydrolyzed to give the corresponding cyclopropylketo- α -methylphenylacetic acid compound of structure (49) as described previously in step
30 c.

In step ii, the carboxy functionality of the appropriate cyclopropylketo- α -methylphenylacetic acid compound of structure (49) may be esterified by techniques
35 and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding cyclopropylketo- α -methylphenylacetic acid ester compound of structure (35) as described previously in step d.

In step jj, the nitrile functionality of the appropriate cyclopropyl cyanoethylphenylketone compound of structure (23) is converted to the corresponding carboxy to give the cyclopropylketo- α -methylphenylacetic acid compound of structure (49) as described previously in step e.

In step kk, the amide functionality of the appropriate cyclopropylketo- α -methylphenylacetic acid amide compound of structure (44) is converted to the corresponding acid by acid hydrolysis as is known in the art to give the corresponding cyclopropylketo- α -methylphenylacetic acid compound of structure (49) as described previously in step f.

In addition, step kk and step ee may be combined and the ω' -halo- α' -keto- α -methylphenylacetic acid compound of structure (48) wherein $n = 3$ may be prepared from the corresponding cyclopropylketo- α -methylphenylacetic acid amide compound of structure (44) as described previously in Scheme A, step j.

In step ll, the carboxy functionality of the appropriate cyclopropylketo- α -methylphenylacetic acid compound of structure (49) may be amidated by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding cyclopropylketo- α -methylphenylacetic acid amide compound of structure (44) as described previously in step g.

In step mm, the α -halo functionality of the appropriate cyclopropyl haloethylphenylketone compound of structure (14) is carboxylated to give the corresponding cyclopropylketo- α -methylphenylacetic acid compound of structure (49) as described previously in step h.

In step nn, the appropriate the amide functionality of the appropriate ω' -halo- α' -keto- α -methylphenylacetic acid

amide compound of structure (42) is converted to the corresponding ester to give the ω' -halo- α' -keto- α -methylphenylacetic acid ester compound of structure (33) as
5 described previously in step i.

In step oo, the nitrile functionality of the appropriate ω -halo cyanotolylketone compound of structure (22) is converted to the corresponding ester by reaction
10 with an appropriate C_1 to C_6 alcohol to give the ω' -halo- α' -keto-phenylacetic acid ester compound of structure (34) as described previously in step a.

In step pp, the nitrile functionality of the
15 appropriate ω -halo cyanotolylketone compound of structure (22) is converted to the corresponding amide to give the ω' -halo- α' -keto-phenylacetic acid amide compound of structure (43) wherein R_6 and R_7 are both hydrogen as described previously in step b.

20
In step qq, the carboxy ester functionality of the appropriate ω' -halo- α' -keto-phenylacetic acid ester compound of structure (34) is hydrolyzed to give the corresponding ω' -halo- α' -keto-methylphenylacetic acid
25 compound of structure (50) as described previously in step c.

In step rr, the carboxy functionality of the appropriate ω' -halo- α' -keto-methylphenylacetic acid
30 compound of structure (50) may be esterified by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding ω' -halo- α' -keto-phenylacetic acid ester compound of structure (34) as described previously in step d.

35
Alternatively, step yy and step rr may be combined and the ω' -halo- α' -keto-phenylacetic acid ester compound of structure (34) wherein $n = 3$ may be prepared from the

corresponding ω' -halo- α' -keto-methylphenylacetic acid compound of structure (50) as described previously in step d.

5

Alternatively, step ddd, step yy and step rr may be combined the ω' -halo- α' -keto-phenylacetic acid ester compound of structure (34) wherein $n = 3$ may be prepared from the corresponding cyclopropyl cyanotolylketone compound of structure (24) as described previously in step d.

In step ss, the nitrile functionality of the appropriate ω -halo cyanotolylketone compound of structure (22) is converted to the corresponding carboxy to give the ω' -halo- α' -keto-methylphenylacetic acid compound of structure (50) as described previously in step e.

In step tt, the amide functionality of the appropriate ω' -halo- α' -keto-phenylacetic acid amide compound of structure (43) is converted to the corresponding acid by acid hydrolysis as is known in the art to give the ω' -halo- α' -keto-methylphenylacetic acid compound of structure (50) as described previously in step f.

25

In step uu, the carboxy functionality of the appropriate ω' -halo- α' -keto-methylphenylacetic acid compound of structure (50) may be amidated by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding ω' -halo- α' -keto-phenylacetic acid amide compound of structure (43) as described previously in step g.

In step vv, the α -halo functionality of the appropriate ω -halo halotolylketone compound of structure (13) is carboxylated to give the corresponding ω' -halo- α' -keto-methylphenylacetic acid compound of structure (50) as described previously in step h.

35

In step ww, the appropriate the amide functionality of the appropriate ω' -halo- α' -keto-phenylacetic acid amide compound of structure (43) is converted to the corresponding ester to give the ω' -halo- α' -keto-phenylacetic acid ester compound of structure (34) as described previously in step i.

10 In step xx, the appropriate ω' -halo- α' -keto-methylphenylacetic acid compound of structure (50) wherein $n = 3$ is ring-closed to give the corresponding cyclopropylketo-phenylacetic acid compound of structure (51) as described previously in Scheme A, step k.

15 In step yy, the appropriate cyclopropylketo-phenylacetic acid compound of structure (51) is ring-opened to give the corresponding ω' -halo- α' -keto-methylphenylacetic acid compound of structure (50) wherein $n = 3$ as described previously in Scheme A, step j.

20 In step zz, the nitrile functionality of the appropriate cyclopropyl cyanotolylketone compound of structure (24) is converted to the corresponding ester by reaction with an appropriate C_1 to C_6 alcohol to give the cyclopropylketo-phenylacetic acid ester compound of structure (36) as described previously in step a.

30 In step aaa, the nitrile functionality of the appropriate cyclopropyl cyanotolylketone compound of structure (24) is converted to the corresponding amide to give the cyclopropylketo-phenylacetic acid amide compound of structure (45) wherein R_6 and R_7 are both hydrogen as described previously in step b.

35 In step bbb, the carboxy ester functionality of the appropriate cyclopropylketo-phenylacetic acid ester compound of structure (36) is hydrolyzed to give the

corresponding cyclopropylketo-phenylacetic acid compound of structure (51) as described previously in step c.

5 In step ccc, the carboxy functionality of the appropriate cyclopropylketo-phenylacetic acid compound of structure (51) may be esterified by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding cyclopropylketo-
10 phenylacetic acid ester compound of structure (36) as described previously in step d.

In step ddd, the nitrile functionality of the appropriate cyclopropyl cyanotolylketone compound of
15 structure (24) is converted to the corresponding carboxy to give the cyclopropylketo-phenylacetic acid compound of structure (51) as described previously in step e.

In step eee, the amide functionality of the appropriate
20 cyclopropylketo-phenylacetic acid amide compound of structure (45) is converted to the corresponding acid by acid hydrolysis as is known in the art to give the corresponding cyclopropylketo-phenylacetic acid compound of structure (51) as described previously in step f.

25 In addition, step yy and step eee may be combined and the ω' -halo- α' -keto-methylphenylacetic acid compound of structure (50) wherein $n = 3$ may be prepared from the corresponding cyclopropylketo-phenylacetic acid amide
30 compound of structure (45) as described previously in Scheme A, step j.

In step fff, the carboxy functionality of the appropriate cyclopropylketo-phenylacetic acid compound of
35 structure (51) may be amidated by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding cyclopropylketo-phenylacetic

-121-

acid amide compound of structure (45) as described previously in step g.

5 In step ggg, the α -halo functionality of the appropriate cyclopropyl halotolylketone of structure (15) is carboxylated to give the corresponding cyclopropylketo-phenylacetic acid compound of structure (51) as described previously in step h.

10 In step hhh, the appropriate the amide functionality of the appropriate cyclopropylketo-phenylacetic acid amide compound of structure (45) is converted to the corresponding ester to give the cyclopropylketo-phenylacetic acid ester compound of structure (36) as
15 described previously in step i.

Starting materials for use in Scheme H are readily available to one of ordinary skill in the art.

20 The following examples present typical syntheses as described in Scheme H. These examples are understood to be illustrative only and are not intended to limit the scope of the present invention in any way. As used herein, the
25 following terms have the indicated meanings: "g" refers to grams; "mmol" refers to millimoles; "mL" refers to milliliters; "bp" refers to boiling point; "°C" refers to degrees Celsius; "mm Hg" refers to millimeters of mercury; "μL" refers to microliters; "μg" refers to micrograms; and
30 "μM" refers to micromolar.

Example 24

Step a: 2-[4-(4-Chloro-butyryl)-phenyl]-2-methyl-propionic acid, methyl ester

35 Place anhydrous methanol (5mL) under argon, cool to 0°C and add hydrogen chloride until saturated. Add 2-[4-(4-chloro-butyryl)-phenyl]-2-methyl-propionitrile (103mg, 4.12mmol), remove the ice bath and stir for 5 hours at room temperature. Allow to stand at -10°C overnight, and stir

-122-

an additional 3 hours at room temperature. Pour into cracked ice (20g) and allow to stand for 5 minutes. Evaporate the solvent *in vacuo* to 1/2 volume, dilute with
5 water and extract with methylene chloride (3X). Combine the organic layers, wash with saturated sodium hydrogen carbonate and brine. Dry (MgSO₄), filter and evaporate the solvent *in vacuo*. Extract the residue into hot hexane (12mL), filter hot and evaporate the solvent *in vacuo* to give
10 the title compound as a colorless oil (97mg, 83%).

Example 25

Step d: 2-[4-(4-Chloro-butyryl)-phenyl]-2-methyl-propionic acid, ethyl ester

15 Add anhydrous hydrogen chloride gas (18.0g) to anhydrous ethanol DB (210g) by purging the solution. Add this hot solution (60°C) to a solution of 2-[4-(4-chloro-butyryl)-phenyl]-2-methyl-propionic acid (31g, 115.6mmol) and reflux under a nitrogen atmosphere for 2.5 hours. Evaporate the
20 solvent *in vacuo*, dissolve the residue in methylene chloride (150mL) and wash with water (2X100mL). Dry (MgSO₄), filter through silica gel, washing the gel with methylene chloride (250mL). Combine the organic washings and evaporate the solvent *in vacuo* to give the title compound as a colorless
25 oil (33.3g, 97%).

¹H NMR (300MHz, CDCl₃) δ 7.96 (d, J=8.3Hz, 2H), 7.45 (d, J=8.3Hz, 2H), 4.15 (q, J=7.1Hz, 2H), 3.70 (t, J=6.6Hz, 2H), 3.19 (t, J=6.8Hz, 2H), 2.25 (p, J=6.6Hz, 2H), 1.61 (s, 6H),
30 1.20 (q, J=7.1Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 198.4, 176.0, 150.3, 135.1, 128.1, 126.0, 61.0, 46.8, 44.6, 35.2, 26.7, 26.3, 14.0; IR (neat) 2978, 1728, 1686, 1606, 1254, 1231, 1148, 1097 cm⁻¹.

35 Anal. Calcd for C₁₆H₂₁O₃Cl: C, 64.75; H, 7.13;
Found: C, 64.24; H, 7.18.

Example 26

Step d: 2-[4-(4-Chloro-butyryl)-phenyl]-2-methyl-propionic acid, methyl ester

Dissolve 2-[4-(4-chloro-butyryl)-phenyl]-2-methyl-propionic
5 acid (6.2g, 23.1mmol) in hot methanolic solution of
anhydrous hydrogen chloride (42mL of a methanol containing
3.2g of anhydrous hydrogen chloride). Reflux for 42
minutes, evaporate the solvent *in vacuo*, dissolve the residue
in methylene chloride and wash with water. Dry (MgSO₄),
10 filter through silica gel, washing the gel with methylene
chloride. Combine the organic washings and evaporate the
solvent *in vacuo* to give the title compound as a clear oil
(6.21g, 94%).

15 ¹H NMR (30MHz, CDCl₃) δ 7.95 (d, J=8.5Hz, 2H), 7.44 (d,
J=8.5Hz, 2H), 3.66 (s, 3H), 3.67 (t, J=6.6Hz, 2H), 3.17 (t,
J=6.6Hz, 2H), 2.30 (p, J=6.6Hz, 2H), 1.61 (s, 6H); ¹³C NMR
(75 MHz, CDCl₃) δ 198.0, 176.2, 149.8, 135.0, 128.0, 125.8,
52.4, 46.9, 44.7, 35.3, 26.8, 26.5.

20

Anal. Calcd for C₁₅H₁₉O₃Cl: C, 63.72; H, 6.77;
Found: C, 63.50; H, 6.67.

Example 27

25 Step d: 2-[4-(4-Chloro-butyryl)-phenyl]-2-methyl-propionic acid, methyl ester

Mix 2-[4-(4-chloro-butyryl)-phenyl]-2-methyl-propionic acid
(10.0g, 37.3mmol) and anhydrous potassium carbonate (3.5g,
25.3mmol). Heat to 40°C in acetonitrile (100mL) and stir
30 under a nitrogen atmosphere. Add dimethyl sulfate (13.3g,
105mmol) and reflux for 45 minutes. Evaporate the solvent
in vacuo, dissolve the residue in ethyl acetate (50mL) and
wash with water (4X50mL). Dry (MgSO₄), filter through
silica gel and evaporate the solvent *in vacuo* to give the
35 title compound (6.4g, 89%).

Example 28

Step h: 2-[4-(4-Chloro-butyryl)-phenyl]-2-methyl-propionic acid

Fit a jacketed glass cell of about 6L capacity with a
5 rotating expanded silver mesh cathode/magnesium anode
assembly, a carbon dioxide delivery tube, and a stainless
steel thermocouple. Load the cell with acetonitrile (5.8L)
and tetraethylammonium bromide (26g). Sparge with carbon
dioxide and cool in cooling bath. When the contents of the
10 cell reach -10°C, add hydrogen chloride remediated 1-[4-(1-
bromo-1-methyl-ethyl)-phenyl]-4-chloro-butan-1-one and 1-
[4-(1-chloro-1-methyl-ethyl)-phenyl]-4-chloro-butan-1-one
(424.9g, 53.5 mole % bromo and 20.4 mole % chloro by HPLC
analysis, 1087 mmol total active tertiary benzylic halide)
15 and perform electrolysis at a controlled current of 8 amps
(20 mA cm⁻²) for 6 hours. Drain the contents, acidify with
chilled aqueous 6M hydrochloric acid, extract, evaporate
the solvent *in vacuo* and recrystallize to give the title
compound (186g, 64%); 78.5-80.3°C.

20

¹H NMR (300MHz, CDCl₃) δ 10.5 (br s, 2H), 7.96 (d, J=8.2Hz, 2H), 7.50 (d, J=8.2Hz, 2H), 3.67 (t, J=6.8Hz, 2H), 3.17 (t, J=6.8Hz, 2H), 2.22 (m, J=6.7Hz, 2H), 1.63 (s, 6H); ¹³C NMR (75MHz, CDCl₃) δ 198.2, 181.9, 149.0, 135.2, 128.1, 126.1,
25 46.7, 44.7, 35.3, 26.9, 26.7; MS (CIMS (Methane)) 271 (3), 269 (11), 233 (100), 187 (75).

Anal. Calcd for C₁₄H₁₇O₃Cl: C, 62.57; H, 6.38;
Found: C, 63.10; H, 6.59.

30

Example 29

Step h: 2-[4-(4-Chloro-butyryl)-phenyl]-2-methyl-propionic acid

Fit a jacketed glass cell of about 50mL capacity with an
35 expanded silver mesh cathode (14 cm² geometric area), a
roughly concentric magnesium sacrificial anode, a tube to
deliver carbon dioxide gas and a magnetic stir bar. Add a
solution of hydrogen chloride remediated 1-[4-(1-bromo-1-

- methoxy-ethyl)-phenyl]-4-chloro-butan-1-one and 1-[4-(1-chloro-1-methoxy-ethyl)-phenyl]-4-chloro-butan-1-one (2.79g, 89 mole %), 3:1 ratio of tertiary benzylic bromide to tertiary benzylic chloride by NMR, approximately 8.6mmol total active tertiary benzylic halide) in acetonitrile (45mL) and tetraethylammonium bromide (0.19g). Close the cell and cool to -10°C with a continuous carbon dioxide sparge for 169 minutes at an average current density of 13 mA cm⁻². Warm to contents of the cell to ambient temperature, drain the contents, acidify with chilled aqueous 6M hydrochloric acid, extract and evaporate the solvent *in vacuo* to give the title compound (1.53g, 66%).

15

Example 30Step h: 2-[4-(4-Chloro-butyryl)-phenyl]-2-methyl-propionic acid

- Fit a jacketed glass cell of 50mL capacity with an expanded silver mesh cathode (14 cm² geometric area), a roughly concentric magnesium sacrificial anode, a tube to deliver carbon dioxide gas, and a magnetic stir bar. Cool the cell to -10°C under carbon dioxide. Add a solution of tetraethylammonium chloride (40mL of a 0.02M solution in dimethylformamide) and 1-[4-(1-chloro-1-methoxy-ethyl)-phenyl]-4-chloro-butan-1-one (2.91g, 85% pure by NMR, 9.81mmol) and carry out electrolysis for 178 minutes at an average current density of 12.4 mA cm⁻²: the total charge passed is equal to 98% of the calculated theoretical two electron value. Warm the contents of the cell to ambient temperature, drain the contents, acidify with chilled aqueous 6M hydrochloric acid, extract and evaporate the solvent *in vacuo* to give the title compound (1.89g, 72%).

Example 31

- 35 Step m: 2-(4-Cyclopropanecarbonyl-phenyl)-2-methyl-propionamide

Dissolve 2-(4-cyclopropanecarbonyl-phenyl)-2-methyl-propionitrile (100mg) in aqueous ethanolic potassium

-126-

- hydroxide (2mL) (prepared from ethanol (5mL), water (5mL) and solid potassium hydroxide (1.5g). Stir overnight at room temperature, then heat at reflux for 6 hours. Cool and evaporate the solvent *in vacuo* to give the title compound.

Example 32

- Step t: 2-(4-Cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid, ethyl ester
- 10 Dissolve 2-(4-cyclopropanecarbonyl-phenyl)-2-methyl-propionamide (100mg) in ethanol and bubble in hydrochloride gas for 5 minutes while stirring. Reflux for 10 hours, distill off the ethanol and extract into ethyl acetate.
- 15 Evaporate the solvent *in vacuo* to give the title compound as an oil (50mg).

Example 33

- Step k and step q: 2-[4-(4-Bromo-butyryl)-phenyl]-2-methyl-propionic acid
- 20 Treat 2-(4-cyclopropanecarbonyl-phenyl)-2-methyl-N-methyl-N-methoxy-propionamide (0.15g, 0.53mmol) with 48% HBr (1mL) for 2 hours at 80°C. Cool to room temperature, dilute with water (5mL) and neutralize with aqueous sodium hydrogen carbonate until pH 7. Extract with methylene chloride (3X15mL), dry (Na₂SO₄), filter and evaporate the solvent *in vacuo*. Purify by silica gel chromatography (3:1 hexane/ethyl acetate) to give the title compound (0.15g, 95%).
- 30
- ¹H NMR (CDCl₃) δ 7.97 (d, 2H), 7.51 (d, 2H), 3.53 (t, 2H), 3.16 (t, 2H), 2.30 (quin, 2H), 1.60 (s, 6H); ¹³C NMR (CDCl₃) δ 198.4, 181.8, 149.5, 131.0, 128.3, 126.3, 46.6, 36.5, 33.6, 26.9, 26.1; MS (CI) (M⁺+H) 303 (100), 315 (98), 233 (80).
- 35

Example 34

Step p: 2-(4-Cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid

Combine 2-(4-cyclopropanecarbonyl-phenyl)-2-methyl-propionitrile (0.5g) in 12.5% sodium hydroxide (20mL) and ethanol (12.5mL). Heat to reflux for 21 hours, cool and remove the ethanol by vacuum distillation. Extract the residual aqueous suspension with methylene chloride (40mL), acidify the aqueous phase with 20% HCl and extract with methylene chloride (2X40mL). Combine the organic phases, dry (Na₂SO₄) and evaporate the solvent *in vacuo* to give the title compound as a crystalline solid (350mg, 70%); mp 83-85°C.

¹H NMR (CDCl₃) δ 7.50-8.00 (4H, d), 2.66 (1H, m), 1.62 (6H, s), 1.24 (2H, m), 1.04 (2H, m).

The following compounds can be prepared by using the procedures depicted in Scheme H:

20

(4-Cyclopropanecarbonyl-phenyl)-acetic acid;

2-(4-Cyclopropanecarbonyl-phenyl)-propionic acid;

25 2-(4-Cyclopropanecarbonyl-phenyl)-2-methyl-propionic acid;

[4-(4-Chloro-butyryl)-phenyl]-acetic acid;

2-[4-(4-Chloro-butyryl)-phenyl]-propionic acid;

30

2-[4-(4-Chloro-butyryl)-phenyl]-2-methyl-propionic acid;

(4-Cyclopropanecarbonyl-phenyl)-acetic acid, ethyl ester;

35 2-(4-Cyclopropanecarbonyl-phenyl)-propionic acid, ethyl ester;

[4-(4-Chloro-butyryl)-phenyl]-acetic acid, ethyl ester;

2-[4-(4-Chloro-butyryl)-phenyl]-propionic acid, ethyl ester;

5

2-[4-(4-Chloro-butyryl)-phenyl]-2-methyl-propionic acid, ethyl ester;

(4-Cyclopropanecarbonyl-phenyl)-acetamide;

10

2-(4-Cyclopropanecarbonyl-phenyl)-propionamide;

[4-(4-Chloro-butyryl)-phenyl]-acetamide;

15 2-[4-(4-Chloro-butyryl)-phenyl]-propionamide; and

2-[4-(4-Chloro-butyryl)-phenyl]-2-methyl-propionamide.

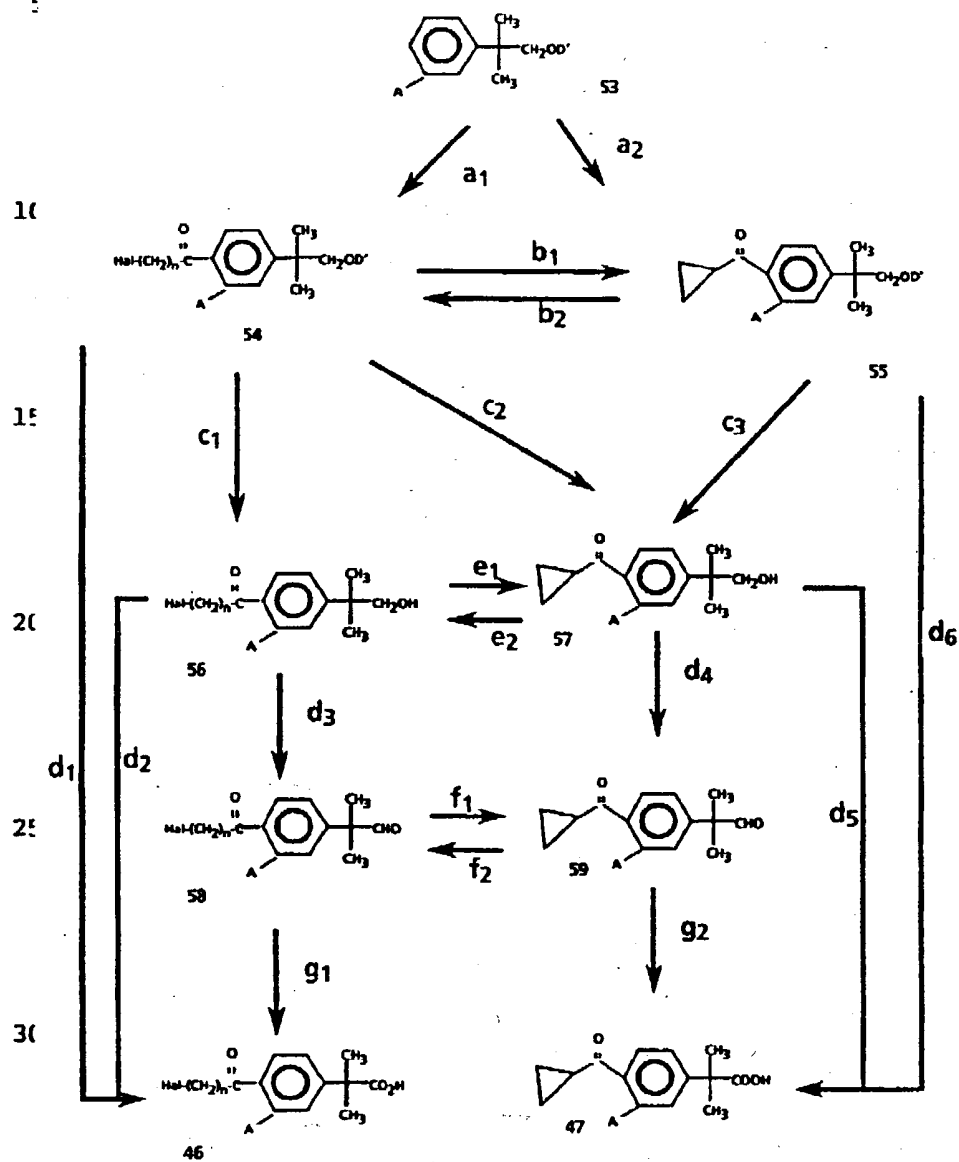
In addition, the novel intermediate of formula (II)
20 wherein R₅ is COOH may be prepared as described in Scheme I.
In Scheme I, all substituents are as previously defined
unless otherwise indicated.

25

30

35

Scheme I



30 D' = -C(=O)CH₃ or -C(=O)C₆H₅

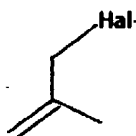
Scheme I provides a general synthetic procedure for preparing the novel intermediate of formula (II) wherein R_5 is COOH.

5

In step a, the neophyl acetate of benzoate of structure (53) is acylated with an appropriate ω -halo compound of the structure $\text{Hal}-(\text{CH}_2)_n-\text{C}(=\text{O})-\text{B}$, wherein B is Hal or hydroxy, Hal is Cl, Br or I and n is as previously defined to give the corresponding ω' -halo- α' -keto-(2-methylpropanol)benzene acetate or benzoate compound of structure (54) as described previously in Scheme A, step d.

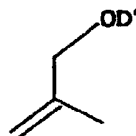
The neophyl acetate of benzoate of structure (53) is prepared by reacting a methallyl halide of structure

20



wherein Hal is Cl, Br or I with sodium acetate or sodium benzoate in a suitable organic solvent such as 1-methyl-2-pyrrolidinone. The reactants are heated at a temperature of approximately 100 to 130°C and the corresponding to give the methallyl acetate or benzoate of structure

30



wherein D' is $-\text{C}(=\text{O})\text{CH}_3$ or $-\text{C}(=\text{O})\text{C}_6\text{H}_5$ which is collected by distillation.

35

A benzene compound of structure

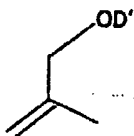
-131-



5

wherein A is defined above is then alkylated with the methylallyl acetate or benzoate of structure

10

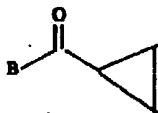


15

wherein D' is $-\text{C}(=\text{O})\text{CH}_3$ or $-\text{C}(=\text{O})\text{C}_6\text{H}_5$ to give the neophyl acetate or benzoate of structure (53) as described previously in Scheme A, step d.

20

In step a₂, the neophyl acetate or benzoate of structure (53) is acylated with an appropriate cyclopropyl compound of the structure



25

wherein B is as previously defined to give the corresponding cyclopropyl neophyl acetate or benzoate of structure (55) as described previously in Scheme A, step e.

30

In step b₁, the appropriate ω' -halo- α' -keto-(2-methylpropanol)benzene acetate or benzoate compound of structure (54) wherein n = 3 is ring-closed to give the corresponding cyclopropyl neophyl acetate or benzoate of structure (55) as described previously in Scheme A, step k.

35

In step b₂, the appropriate cyclopropyl neophyl acetate or benzoate of structure (55) is ring-opened to give the corresponding ω' -halo- α' -keto-(2-methylpropanol)benzene

acetate or benzoate compound of structure (54) wherein $n = 3$ as described previously in Scheme H, step j.

5 In step c_1 , the acetate or benzoate functionality of the appropriate ω' -halo- α' -keto-(2-methylpropanol)benzene acetate or benzoate compound of structure (54) is hydrolyzed with concentrated hydrochloric acid in ethanol at reflux temperature for a period of time ranging from 1-
10 10 hours. The corresponding ω' -halo- α' -keto-(2-methylpropanol)benzene compound of structure (56) is recovered from the reaction zone by extractive methods as is known in the art.

15 In step c_2 , the appropriate ω' -halo- α' -keto-(2-methylpropanol)benzene acetate or benzoate compound of structure (54) wherein $n = 3$ is ring closed and the acetate or benzoate functionality hydrolyzed with base to give the cyclopropyl neophyl alcohol compound of structure (57).

20 For example, the appropriate ω' -halo- α' -keto-(2-methylpropanol)benzene acetate or benzoate compound of structure (54) wherein $n = 3$ is reacted with 40% aqueous tetrabutylammonium hydroxide and 50% aqueous sodium
25 hydroxide at reflux temperature for a period of time ranging from 5-72 hours. The cyclopropyl neophyl alcohol compound of structure (57) may be recovered from the reaction zone by extractive methods as are known in the art.

30 In step c_3 , the acetate or benzoate functionality of the appropriate cyclopropyl neophyl acetate or benzoate of structure (55) is hydrolyzed to give the corresponding cyclopropyl neophyl alcohol of structure (57).

35 For example, the appropriate cyclopropyl neophyl acetate or benzoate of structure (55) is reacted with 50% aqueous sodium hydroxide at reflux temperature for a period

of time ranging from 5 minutes to 5 hours. The corresponding cyclopropyl neophyl alcohol of structure (57) is recovered from the reaction zone by extractive methods as are known in the art.

In step d₁, the ω' -halo- α' -keto-(2-methylpropanol)benzene acetate or benzoate compound of structure (54) is converted to the corresponding ω' -halo- α' -keto- α,α -dimethylphenylacetic acid compound of structure (46).

For example, the appropriate cyclopropyl neophyl alcohol of structure (54) may be reacted with ruthenium chloride/sodium periodate in a suitable organic solvent such as acetonitrile and/or carbon tetrachloride, ruthenium chloride/sodium hypochloride in a suitable solvent such as acetic acid/water, potassium permanganate in a suitable solvent such as acetic acid/water, fuming nitric acid in acetic acid or sodium nitrite/concentrated nitric acid in acetic acid. The reactants are typically mixed stirred together at a temperature range of 10°C to 50°C and for a period of time ranging from 30 minutes to 10 hours. The corresponding cyclopropylketo- α,α -dimethylphenylacetic acid compound of structure (46) is recovered from the reaction zone by extractive methods as is known in the art.

In step d₂, the ω' -halo- α' -keto-(2-methylpropanol)benzene compound of structure (56) is converted to the corresponding ω' -halo- α' -keto- α,α -dimethylphenylacetic acid compound of structure (46).

For example, the appropriate ω' -halo- α' -keto-(2-methylpropanol)benzene compound of structure (56) may be oxidized with potassium permanganate in suitable acid solvent such as acetic acid. The reactants are typically reacted at a temperature range of from about 0°C to 5°C for a period of time ranging from 30 minutes to 10 hours.

-134-

The corresponding ω' -halo- α' -keto- α,α -dimethylphenylacetic acid compound of structure (46) is recovered from the reaction zone by extractive methods as are known in the art and may be purified by recrystallization. Other oxidizing reagents suitable for the oxidation of the appropriate ω' -halo- α' -keto-(2-methylpropanol)benzene compound of structure (56) to the corresponding ω' -halo- α' -keto- α,α -dimethylphenylacetic acid compound of structure (46) are nitric acid, chromium (IV) oxide, nitrogen dioxide, ruthenium (VIII) oxide, nickel peroxide, silver oxide, t-butyl chromate, xenic acid

In step d₃, the hydroxymethyl functionality of the appropriate ω' -halo- α' -keto-(2-methylpropanol)benzene compound of structure (56) is oxidized with a variety of oxidizing agents and methods to give the corresponding ω' -halo- α' -keto- α,α -dimethylphenylacetaldehyde compound of structure (58).

20

One such method involves a procedure in which the hydroxymethyl functionality of the appropriate ω' -halo- α' -keto-(2-methylpropanol)benzene compound of structure (56) is oxidized to the corresponding aldehyde functionality using, for example, Swern Oxidation conditions (dimethyl sulfoxide, oxalyl chloride and triethylamine), as is known in the art. The Swern Oxidation is carried out in a suitable aprotic organic solvent such as methylene chloride at temperatures ranging from about -78°C to room temperature, and the reaction time varies from about 1/2 hours to 8 hours. Other suitable reagents for the oxidation of the hydroxyethyl functionality of the appropriate ω' -halo- α' -keto-(2-methylpropanol)benzene compound of structure (56) to the corresponding ω' -halo- α' -keto- α,α -dimethylphenylacetaldehyde compound of structure (58) are Dess-Martin reagent, chromium (IV) oxide, nickel peroxide, sodium dichromate, potassium dichromate, t-butyl chromate, silver oxide, argentic picolinate, manganese

dioxide, lead tetraacetate, dicyclohexylcarbodiimide, 2,3-dichloro-5,6-dicyanoquinone, tetrachloro-1,2-benzoquinone, 2,2,6,6-tetramethylpiperidiny-1-oxy (TEMPO) or quinolinium
5 chlorochromate.

In step d₄, the hydroxymethyl functionality of the appropriate cyclopropyl neophyl alcohol of structure (57) is oxidized to give the corresponding cyclopropylketo- α,α -
10 dimethylphenylacetaldehyde compound of structure (59) as described previously in step d₃.

In step d₅, the appropriate cyclopropyl neophyl alcohol of structure (57) is converted to the corresponding
15 cyclopropylketo- α,α -dimethylphenylacetic acid compound of structure (47) as described previously in step d₂.

In step d₆, the appropriate cyclopropyl neophyl acetate or benzoate of structure (55) is converted to the
20 corresponding cyclopropylketo- α,α -dimethylphenylacetic acid compound of structure (47) as described previously in step d₁.

In step e₁, the appropriate ω' -halo- α' -keto-(2-methylpropanol)benzene compound of structure (56) wherein n
25 = 3 is ring-closed to give the corresponding cyclopropyl neophyl alcohol of structure (57) as described previously in Scheme H, step j.

In step e₂, the appropriate cyclopropyl neophyl alcohol of structure (57) is ring-opened to give the corresponding
30 ω' -halo- α' -keto-(2-methylpropanol)benzene compound of structure (56) wherein n = 3 as described previously in Scheme H, step k.

35

In step f₁, the appropriate ω' -halo- α' -keto- α,α -dimethylphenylacetaldehyde compound of structure (58) wherein n = 3 is ring-closed to give the corresponding

cyclopropylketo- α,α -dimethylphenylacetaldehyde compound of structure (59) as described previously in Scheme H, step j.

5 In step f_2 , the appropriate cyclopropylketo- α,α -dimethylphenylacetaldehyde compound of structure (59) is ring-opened to give the corresponding ω' -halo- α' -keto- α,α -dimethylphenylacetaldehyde compound of structure (58) wherein $n = 3$ as described previously in Scheme H, step k.

10

In step g_1 , the aldehyde functionality of the appropriate ω' -halo- α' -keto- α,α -dimethylphenylacetaldehyde compound of structure (58) is oxidized to give the corresponding ω' -halo- α' -keto- α,α -dimethylphenylacetic acid
15 compound of structure (46).

For example, the appropriate ω' -halo- α' -keto- α,α -dimethylphenylacetaldehyde compound of structure (58) is reacted with, for example, potassium permanganate. The
20 potassium permanganate oxidation is carried out in a suitable acidic medium such as hydrochloric acid/acetone at a temperature ranging from about 0°C to room temperature and the reaction time varies from about 1/2 hour to 8 hours. Other suitable reagents for the oxidation of the
25 ω' -halo- α' -keto- α,α -dimethylphenylacetaldehyde compound of structure (58) to the corresponding ω' -halo- α' -keto- α,α -dimethylphenylacetic acid compound of structure (46) are chromium (IV) oxide, silver (I) oxide, silver oxide, argentic picolinate, peroxide, nitric acid, m-
30 chloroperbenzoic acid and peracetic acid.

In step g_2 , the aldehyde functionality of the appropriate cyclopropylketo- α,α -dimethylphenylacetaldehyde compound of structure (59) is oxidized to give the
35 corresponding cyclopropylketo- α,α -dimethylphenylacetic acid compound of structure (47) as described previously in step g_1 .

Starting materials for use in Scheme I are readily available to one of ordinary skill in the art.

5 The following examples present typical syntheses as described in Scheme I. These examples are understood to be illustrative only and are not intended to limit the scope of the present invention in any way. As used herein, the following terms have the indicated meanings: "g" refers to
10 grams; "mmol" refers to millimoles; "mL" refers to milliliters; "bp" refers to boiling point; "°C" refers to degrees Celsius; "mm Hg" refers to millimeters of mercury; "μL" refers to microliters; "μg" refers to micrograms; and "μM" refers to micromolar.

15

Example 35

Step a₁: 2-(4-(4-Chloro-1-oxo-butyl))-phenyl-2-methyl propanyl acetate

20 Mix 1-methyl-2-pyrrolidinone (400mL), sodium acetate (205g, 2.5mol), stir at heat to 100°C in a reaction flask which is fitted with a distillation head. Add, by dropwise addition, methylallyl chloride (181g, 2.0mol) over 1 hour. Heat the pot to 120°C for 30 minutes collect methallyl
25 acetate by distillation (193g).

Mix methallyl acetate (228g, 2.0mol) and benzene (1L) and cool to 5°C. Add aluminum chloride (266g, 2.0mol) over approximately 30 minutes while maintaining the temperature
30 below 10°C. Add, in portions of 50mL to 80mL each, to a 5°C mixture of aluminum chloride (15g) in benzene (600mL). After addition is complete, stir at 0-3°C for 1/2 hour, pour onto ice (2kg) and separate the organic layer. Wash with water (2X300mL), dry (Na₂SO₄), and distill to give
35 neophyl acetate.

Dissolve neophyl acetate (150g, 0.78mol) in methylene chloride (390mL) and cool to 5°C. Add anhydrous aluminum

-138-

chloride (104g, 0.78mol) at such a rate that the temperature is maintained below 10°C. Cool the reaction mixture to 5°C. Dissolve anhydrous aluminum chloride (122g) in methylene chloride (390mL) and cool to 5°C. Add 4-chlorobutyryl chloride (132g, 0.94mol) at such a rate that the temperature is kept below 10°C. Cool the reaction to 5°C and add the neophyl acetate-aluminum chloride solution in one portion and stir between -5°C and 5°C for 19 hours. Pour slowly over crushed ice (1.5kg), separate the organic phase and wash with water (3X300mL), cold aqueous potassium carbonate (10%, 300mL) and water (300mL). Evaporate the solvent *in vacuo* and filter to give the title compound as a light-brown oil (221.1g, 95.6%).

¹H NMR (300MHz, CDCl₃) δ 1.34 (6H, s), 1.95 (3H, s), 2.18 (2H, quent.), 3.13 (2H, t), 3.65 (2H, t), 4.12 (2H, s), 7.43, 7.90 (2H each, d).

20

Example 36

Step b₁: 2-(4-(1-Oxo-1-cyclopropanyl)-phenyl-2-methylpropanyl acetate

Mix 2-(4-(4-chloro-1-oxo-butyl))-phenyl-2-methyl propanyl acetate (37.0g, 0.125mol), tetrabutylammonium hydroxide (8.1g of a 40% aqueous solution), methylene chloride (300mL) and 50% sodium hydroxide (40mL). Stir vigorously at room temperature for 4 hours, add water (100mL) and separate the organic layer. Wash with water (2X100mL), dry (MgSO₄) and evaporate the solvent *in vacuo* to give the title compound (29.9g).

¹H NMR (300MHz, CDCl₃) δ 1.00, 1.19 (2H each, m), 1.34 (6H, s), 1.95 (3H, s), 2.65 (1H, m), 4.13 (2H, s), 7.44, 7.95 (2H each, d).

Example 37

Step c₁: 2-(4-(4-Chloro-1-oxobutyl))-phenyl-2-methylpropanol
Mix 2-(4-(4-chloro-1-oxo-butyl))-phenyl-2-methyl propanyl
acetate, concentrated hydrochloric acid (555mL), and
5 ethanol (2.5L) and reflux for 2.5 hours under a nitrogen
atmosphere. Evaporate the solvent *in vacuo* and take the
residue up in methylene chloride (1L). Wash sequentially
with water (2X400mL), aqueous potassium carbonate (10%,
200mL) and water (300mL). Evaporate the solvent *in vacuo* to
10 give the title compound as a light-brown oil (200g, 90%).

¹H NMR (300MHz, CDCl₃) δ 1.35 (6H, s), 2.21 (2H, quent.)
3.15, (2H, t), 3.64 (2H, s), 3.66 (2H, s), 7.48, 7.93 (2H
each, d).

15

Example 38

Step c₂: 2-(4-(1-Oxo-1-cyclopropanyl))-phenyl-2-
methylpropanol
20 Mix 2-(4-(4-chloro-1-oxobutyl))-phenyl-2-methylpropanol
(101g, 0.34mol), methylene chloride (800mL), 40% aqueous
solution of tetrabutylammonium hydroxide (33g), and 50%
aqueous solution of sodium hydroxide (162mL) and reflux for
48 hours. Add water (300mL), separate the organic phase
25 and wash with water (2X300mL). Dry (MgSO₄) and evaporate
the solvent *in vacuo* to give the title compound as a light-
brown oil (71.1g, 96%).

Example 39

30

Step c₃: 2-(4-(1-Oxo-1-cyclopropanyl))-phenyl-2-
methylpropanol
Mix 2-(4-(1-oxo-1-cyclopropanyl))-phenyl-2-methylpropanyl
acetate (4.16g, 14mmol), ethanol (50mL) and water (5mL).
35 Add 50% aqueous sodium hydroxide (4.48mL, 56mmol). Stir
and heat at reflux for 30 minutes then remove the ethanol *in*
vacuo. Extract the aqueous residue with methylene chloride
(2X25mL), wash with water (2X25mL), dry (MgSO₄) and

evaporate the solvent *in vacuo* to give the title compound as a brown oil (2.91g, 95.3%).

- 5 ¹H NMR (300MHz, CDCl₃) δ 1.03, 1.20 (2H each, m), 1.35 (6H, s), 1.70 (1H, t, br), 2.66 (1H, m), 3.64 (2H, d), 7.48, 7.98 (2H each, d).

Example 40

10

Step d₂: 2-(4-(4-Chloro-2-oxo-butyl))-phenyl-2-methylpropionic acid

- Mix powdered potassium permanganate (39.5g, 0.25mol), water (34mL) and acetic acid (200mL). Stir and cool at 0°C, then
15 add 85% phosphoric acid (4.2g). Stir vigorously and add 2-(4-(4-chloro-1-oxo-butyl))-phenyl-2-methylpropanol (24.5g, 0.1mol) in acetic acid (50mL) at such a rate as to keep the temperature below 5°C. Stir for 5.5 hours below 5°C, add ice water (300mL), then sodium metabisulfite (45g) in small
20 portions until the dark brown mixture becomes colorless. Extract the aqueous solution with methylene chloride (3X150mL), wash with water (100mL) then extract with 20% aqueous potassium carbonate (2X150mL). Wash the aqueous phase with methylene chloride (50mL), cool in an ice-bath
25 and acidify carefully with concentrated hydrochloric acid until pH 3. Extract with methylene chloride (2X150mL), wash with water (2X80mL) and dry (MgSO₄). Evaporate the solvent *in vacuo* to give the title compound as a crystalline solid (21.25g).

30

¹H NMR (300MHz, CDCl₃) δ 1.63 (6H, s), 2.22 (2H, quent.), 3.17 (2H, t), 3.67 (2H, t), 7.50, 7.92 (2H each, d), 12.3 (1H, s, br).

35

Example 41

Step d₅: 2-(4-(1-Oxo-1-cyclopropanyl))-phenyl-2-methylpropionic acid

Method A:

- Mix 2-(4-(1-oxo-1-cyclopropanyl))-phenyl-2-methylpropanol
5 (1.46g, 6.7mmol), ruthenium chloride (0.036g, 0.17mmol),
acetonitrile (14mL), carbon tetrachloride (14mL) and water
(20mL). Stir vigorously and add sodium periodate (5.85g)
in one portion. Stir at room temperature for one hour
longer, partition between methylene chloride (20mL) and
10 water (5mL), separate the organic layer, extract the
aqueous layer with methylene chloride (15mL) and wash the
combined methylene chloride layers with water (15mL) and
extract with 20% aqueous potassium carbonate (2X25mL).
Cool the base solution in an ice-bath, acidify carefully
15 with concentrated hydrochloride acid to pH 3 and extract
into methylene chloride (2X30mL). Wash with water (15mL),
dry (MgSO₄) and evaporate the solvent *in vacuo* to give the
title compound as a yellow oil (1.41g, 90%).
- 20 ¹H NMR (300MHz, CDCl₃) δ 1.04, 1.23 (2H each, d), 1.63 (6H,
s), 2.65 (1H, m), 7.50, 7.99 (2H each, d).

Method B:

- Mix 2-(4-(1-oxo-1-cyclopropanyl))-phenyl-2-methylpropanol
25 (10.9g, 50mmol), ruthenium chloride (0.032g, 0.16mmol),
acetic acid (100ml) and water (25mL). Cool to 10°C and
add, by dropwise addition, an aqueous solution of sodium
hypochloride (70ml), stirring vigorously over a 30-minute
period. Stir below 10°C for 30 minutes longer, evaporate
30 most of the solvent *in vacuo* and take the residue up in
methylene chloride (120mL). Wash the methylene chloride
solution with water (2X40mL) and extract with 20% aqueous
potassium carbonate (2X50mL). Cool the base solution in an
ice-bath, acidify carefully with concentrated hydrochloride
35 acid to pH 3 and extract into methylene chloride (2X50mL).
Wash the organic layer with water (40mL), dry (MgSO₄) and
evaporate the solvent *in vacuo* to give the title compound as
a light-yellow oil (5.46g, 47%).

Method C:

- Mix potassium permanganate (3.61g, 22.8mmol), water (2mL)
5 and acetic acid (10mL). Stir and cool to 10°C and add 85% phosphoric acid (500mg). Add, by dropwise addition, a solution 2-(4-(1-oxo-1-cyclopropanyl))-phenyl-2-methylpropanol (1.66g, 7.6mmol) in acetic acid (5mL) over 5 minutes. Stir below 10°C for 1 hour and then at room
10 temperature for 5 hours. Add water (20mL) followed by addition of Na₂S₂O₅ in small portions until the solution becomes colorless. Extract with methylene chloride (2X50mL), wash the methylene chloride solution with water (30mL) and then extract with 10% aqueous potassium
15 carbonate (2X50mL). Cool the base solution in an ice-bath, acidify carefully with concentrated hydrochloric acid to pH 3 and extract with methylene chloride (2X50mL). Wash the organic layer with water (20mL), dry (MgSO₄) and evaporate the solvent *in vacuo* to give the title compound as
20 a colorless needles (1.20g, 68%).

¹H NMR (300MHz, CDCl₃) δ 1.00 (4H, d), 1.50 (6H, s), 7.49, 8.00 (2H each, d), 12.6 (1H, s, br).

25 Method D:

- Mix 2-(4-(1-oxo-1-cyclopropanyl))-phenyl-2-methylpropanol (2.30g, 10.6mmol), acetic acid (5.5mL) and fuming nitric acid (6.5mL). Stir and heat at 48-50°C for 2 hours, cool and add ice water (20mL) followed by methylene chloride
30 (60mL). Separate the organic layer, wash with water (2X20mL) and extract into 10% aqueous potassium carbonate (2X40mL). Wash the alkaline solution with methylene chloride (10mL) and cool in an ice-bath. Acidify carefully with concentrated hydrochloric acid to pH 3, extract with
35 methylene chloride (2X40mL), wash the combined organic layers with water (20mL), dry (MgSO₄) and evaporate the solvent *in vacuo* to give the title compound as light-yellow needles (1.89g, 77%).

Method E:

- Mix 2-(4-(1-oxo-1-cyclopropanyl))-phenyl-2-methylpropanol
- 5 (2.26g, 10.4mmol), sodium nitrite (60mg), acetic acid (5mL) and concentrated nitric acid (6mL, d=1.42, 70%, 94mmol). Stir and heat at 48-50°C for 2 hours, cool and dilute with ice water (20mL). Extract into methylene chloride (2X30mL), wash the combined organic layers with water
- 10 (2X20mL) and extract into 10% aqueous potassium carbonate (2X40mL). Wash the alkaline solution with methylene chloride (10mL) and cool in an ice-bath. Acidify carefully with concentrated hydrochloric acid to pH 3 and extract into methylene chloride (2X40mL). Wash the combined
- 15 organic layers with water (20mL), dry (MgSO₄) and evaporate the solvent *in vacuo* to give the title compound as light yellow needles (2.01g, 83%).

Example 42

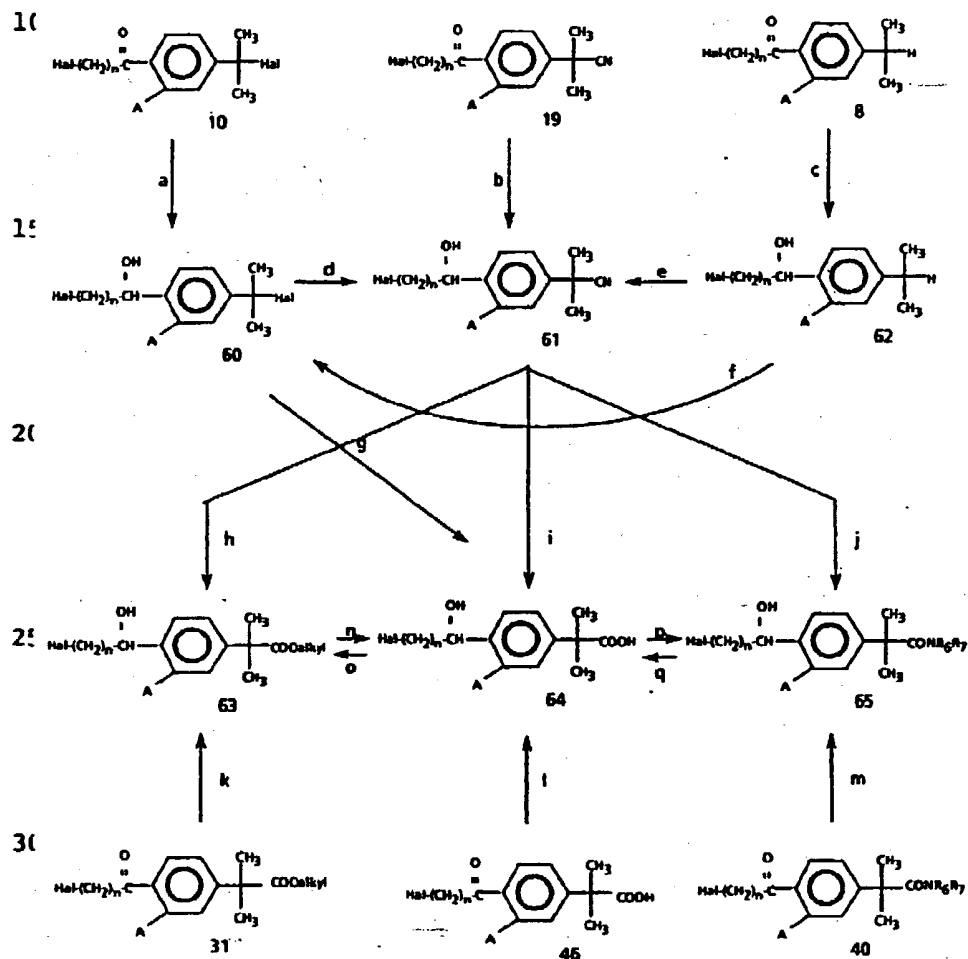
20

Step d₆: 2-(4-(1-oxo-1-cyclopropanyl))-phenyl-2-methylpropionic acid

- Mix 2-(4-(1-oxo-1-cyclopropanyl))-phenyl-2-methylpropanyl acetate (5.0g, 0.0197mol), sodium nitrite (100mg), acetic
- 25 acid (10mL) and concentrated nitric acid (8.7mL, d=1.42, 70%, 0.137mol). Stir and heat at 48-50°C for 5.5 hours, cool and dilute with ice water (40mL). Extract into methylene chloride (2X70mL), wash the combined methylene chloride extracts with water (2X50mL) and reduce the volume
- 30 to 50mL *in vacuo*. Extract with 10% aqueous potassium carbonate (2X50mL), wash the base solution with methylene chloride (20mL) and cool in an ice-bath. Acidify carefully with concentrated hydrochloric acid to pH 3 and extract into methylene chloride (2X60mL). Wash the combined
- 35 methylene chloride extracts with water (30mL), dry (MgSO₄) and evaporate the solvent *in vacuo* to give the title compound as a crystalline solid (4.12g, 90%).

The novel intermediates of formula (X) wherein R_5 is H, Br, Cl, I, CN, $-\text{COOH}$, $-\text{COOalkyl}$ or $-\text{CONR}_6\text{R}_7$ may be prepared as described in Scheme J. In Scheme J, all substituents 5 are as previously defined unless otherwise indicated.

Scheme J



Scheme J provides various general synthetic procedures for preparing the novel intermediates of formula (X) wherein R_5 is H, Br, Cl, I, CN, $-\text{COOH}$, $-\text{COOalkyl}$ or $-\text{CONR}_6\text{R}_7$.

In step a, the ketone functionality of the appropriate ω -halo-halocumylketone compound of structure (10) is
5 reduced to give the corresponding ω -halo-halocumylalcohol compound of structure (60).

For example, reduction of the appropriate ω -halo-halocumylketone compound of structure (10), using, for
10 example, a suitable reducing agent such as sodium borohydride, potassium borohydride, sodium cyanoborohydride, or tetramethylammonium borohydride is carried out in lower alcohol solvents, such as, methanol, ethanol, isopropyl alcohol or n-butanol at temperatures
15 ranging from about 0°C to the reflux temperature of the solvent, and the reaction time varies from about 1/2 hour to 8 hours. Other suitable reducing agents are, for example, lithium tri-tert-butylaluminumhydride and diisobutylaluminum hydride. These reduction reactions are
20 carried out in suitable solvents diethyl ether, tetrahydrofuran or dioxane at temperatures ranging from about 0°C to the reflux temperature of the solvent, and the reaction time varies from about 1/2 hour to 8 hours.

25 Catalytic reduction may also be employed in the preparation of appropriate ω -halo-halocumylalcohol compound of structure (60) from an appropriate ω -halo-halocumylketone compound of structure (10), using hydrogen gas in the presence of a suitable catalyst such as Raney
30 nickel, palladium, platinum or rhodium catalysts in lower alcohol solvents, such as, methanol, ethanol, isopropyl alcohol or n-butanol or acetic acid or their aqueous mixtures, or by the use of aluminum isopropoxide in isopropyl alcohol.

35

In addition, a chiral reduction of the appropriate ω -halo-halocumylketone compound of structure (10), using, for example, (+)- β -chlorodiisopinocampheylborane gives the

corresponding (R)- ω -halo-halocumylalcohol compound of structure (60) and (-)-B-chlorodiisopinocampheylborane gives the corresponding (S)- ω -halo-halocumylalcohol compound of structure (60). Other suitable chiral reducing agents are, (R) and (S)-oxazaborolidine/ BH_3 , potassium 9-O-(1,2:5,6-di-O-isopropylidene- α -D-glucofuransoyl)-9-boratabicyclo[3.3.1]nonane, (R) and (S)-B-3-pinanyl-9-borabicyclo[3.3.1]nonane, NB-Enantride, Lithium (R)-(+), and (S)-(-)-2,2'-dihydroxy-1,1'-binaphthyl alkoxyl aluminum hydride, (R)-(+), and (S)-(-)-2,2'-dihydroxy-6,6'-dimethylbiphenyl borane-amine complex, tris([(1S,2S,5R)-2-isopropyl-5-methyl-cyclohex-1-yl]methyl)aluminum, [(1R,3R)-2,2-dimethylbicyclo[2.2.1]hept-3-yl]methyl]beryllium chloride, (R)-BINAP-ruthenium complex/ H_2 and 6,6'-bis(diphenylphosphino)-3,3'-dimethoxy-2,2',4,4'-tetramethyl-1,1'-biphenyl.

In step b, the ketone functionality of the appropriate ω -halo-cyanocumylketone compound of structure (19) is reduced to give the corresponding ω -halo-cyanocumylalcohol compound of structure (61) as described previously in step a.

In step c, the ketone functionality of the appropriate ω -halo-cyanocumylketone compound of structure (8) is reduced to give the corresponding ω -halo-cyanocumylalcohol compound of structure (62) as described previously in step a.

In step d, the α -halo functionality of the appropriate ω -halo-halocumylalcohol compound of structure (60) is cyanated to give the corresponding ω -halo-cyanocumylalcohol compound of structure (61) as described previously in Scheme D, step a.

In step e, the appropriate ω -halo-cyanocumylalcohol compound of structure (62) is cyanated to give the

corresponding ω -halo-cyanocumylalcohol compound of structure (61) as described previously in Scheme D, step b.

5 In step f, the appropriate appropriate ω -halo-cyanocumylalcohol compound of structure (62) is halogenated to give the corresponding ω -halo-halocumylalcohol compound of structure (60) as described previously in Scheme B, step a.

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In step g, the α -halo functionality of the appropriate ω -halo-halocumylalcohol compound of structure (60) is converted to the corresponding carboxy to give the ω' -halo- α' -hydroxy- α,α -dimethylphenylacetic acid compound of structure (64) as described previously in Scheme H, step h.

20 In step h, the nitrile functionality of the appropriate ω -halo-cyanocumylalcohol compound of structure (61) is converted to the corresponding ester to give the ω' -halo- α' -hydroxy- α,α -dimethylphenylacetic acid ester compound of structure (63) as described previously in Scheme H, step a.

25 In step i, the nitrile functionality of the appropriate ω -halo-cyanocumylalcohol compound of structure (61) is converted to the corresponding acid to give the ω' -halo- α' -hydroxy- α,α -dimethylphenylacetic acid compound of structure (64) as described previously in Scheme H, step e.

30 In step j, the nitrile functionality of the appropriate ω -halo-cyanocumylalcohol compound of structure (61) is converted to the corresponding amide to give the ω' -halo- α' -hydroxy- α,α -dimethylphenylacetic acid amide compound of structure (65) wherein R_6 and R_7 are each hydrogen as described previously in Scheme H, step b.

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In step k, the ketone functionality of the appropriate ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound of structure (31) is reduced to give the

corresponding ω' -halo- α' -hydroxy- α,α -dimethylphenylacetic acid ester compound of structure (63) as described previously in step a.

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In step l, the ketone functionality of the appropriate ω' -halo- α' -keto- α,α -dimethylphenylacetic acid compound of structure (46) is reduced to give the corresponding ω' -halo- α' -hydroxy- α,α -dimethylphenylacetic acid compound of structure (64) as described previously in step a.

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In step m, the ketone functionality of the appropriate ω' -halo- α' -keto- α,α -dimethylphenylacetic acid amide compound of structure (40) is reduced to give the corresponding ω' -halo- α' -hydroxy- α,α -dimethylphenylacetic acid amide compound of structure (65) as described previously in step a.

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In step n, the carboxy ester functionality of the appropriate ω' -halo- α' -hydroxy- α,α -dimethylphenylacetic acid ester compound of structure (63) is hydrolyzed to give the corresponding ω' -halo- α' -hydroxy- α,α -dimethylphenylacetic acid compound of structure (64) as described previously in Scheme H, step c.

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In step o, the carboxy functionality of the appropriate ω' -halo- α' -hydroxy- α,α -dimethylphenylacetic acid compound of structure (64) may be esterified by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding ω' -halo- α' -hydroxy- α,α -dimethylphenylacetic acid ester compound of structure (63) as described previously in Scheme H, step d.

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In step p, the carboxy functionality of the appropriate ω' -halo- α' -hydroxy- α,α -dimethylphenylacetic acid compound of structure (65) may be amidated by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding ω' -halo- α' -

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hydroxy- α,α -dimethylphenylacetic acid amide compound of structure (57) as described previously in Scheme H, step g.

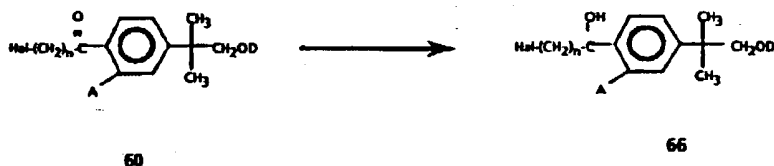
- 5 In step g, the amide functionality of the appropriate ω' -halo- α' -hydroxy- α,α -dimethylphenylacetic acid amide compound of structure (65) is converted to the corresponding acid by acid hydrolysis as is known in the art to give the ω' -halo- α' -hydroxy- α,α -dimethylphenylacetic acid compound of structure (64) as described previously in
10 Scheme H, step f.

In addition, the novel intermediates of formula (X) wherein R_5 is $-\text{CH}_2\text{OD}$ may be prepared as described in Scheme

- 15 K. In Scheme K, all substituents are as previously defined unless otherwise indicated.

Scheme K Cont.

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D = H, $-\text{C}(=\text{O})\text{CH}_3$, $-\text{C}(=\text{O})\text{C}_6\text{H}_5$,

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-150-

In Scheme K, the ketone functionality of the appropriate ω' -halo- α' -keto-(2-methylpropanol)benzene compound of structure (60) is reduced to give the
5 corresponding ω' -halo- α' -hydroxy-(2-methylpropanol)benzene compound of structure (66) as described previously in Scheme J, step a.

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The novel intermediates of formula (XI) wherein R_5 is hydrogen, CN, COOalkyl or CONR₆R₇ may be prepared as described in Scheme L. In Scheme L, all substituents are
5 as previously defined unless otherwise indicated.

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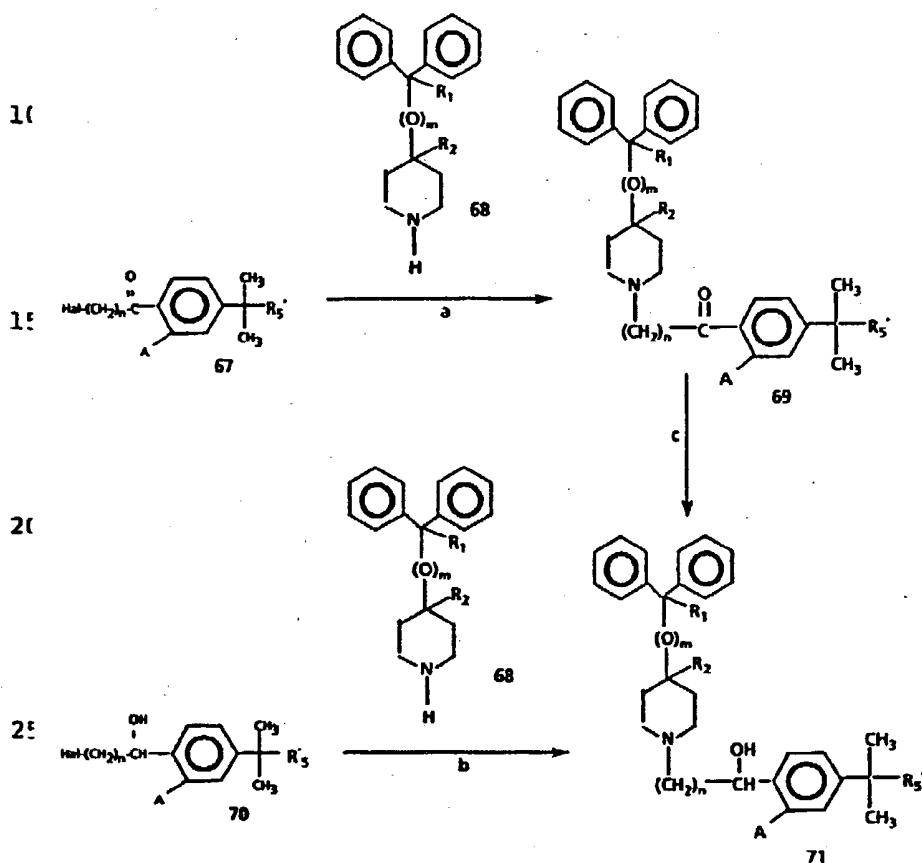
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Scheme L



R_5' is H, CN, COOalkyl or CONR₆R₇

Scheme L provides various general synthetic procedures for preparing the novel intermediates of formula (XI) wherein R_5 is hydrogen, CN, COOalkyl or CONR₆R₇.

In step a, the ω' -halo functionality of the appropriate ω' -halo- α' -keto- α,α -dimethylphenyl compound of structure (67) wherein R_5 is hydrogen, CN, COOalkyl or CONR₆R₇ is alkylated with the appropriate piperidine compound of structure (68) to give the corresponding ω' -piperidine- α' -keto- α,α -dimethylphenyl compound of structure (69) wherein R_5 is hydrogen, CN, COOalkyl or CONR₆R₇.

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For example, the ω' -piperidine- α' -keto- α,α -dimethylphenyl compound of structure (69) wherein R_5 is hydrogen, CN, COOalkyl or CONR₆R₇ may be prepared by reacting the appropriate ω' -halo- α' -keto- α,α -dimethylphenyl compound of structure (67) wherein R_5 is hydrogen, CN, COOalkyl or CONR₆R₇ with the appropriate piperidine compound of structure (68) in a suitable solvent preferably in the presence of a suitable non-nucleophilic base and optionally in the presence of a catalytic amount of an iodide source, such as potassium or sodium iodide. The reaction time varies from about 4 to 120 hours and the reaction temperature varies from about 70°C to the reflux temperature of the solvent. Suitable solvent for the alkylation reaction include alcohol solvents such as, methanol, ethanol, isopropyl alcohol, or n-butanol; ketone solvents, such as, cyclohexanone, methyl isobutyl ketone; hydrocarbon solvents, such as, benzene, toluene or xylene; halogenated hydrocarbons, such as, chlorobenzene or methylene chloride or dimethylformamide. Suitable non-nucleophilic bases for the alkylation reaction include inorganic bases, for example, sodium bicarbonate, potassium carbonate, or potassium bicarbonate or organic bases, such as, a trialkylamine, for example, triethylamine or pyridine, or an excess of an appropriate piperidine compound of structure (68) may be used.

For those piperidine compounds of structure (68), wherein R_1 is hydroxy, it is preferred that R_1 be

unprotected for utilization in the alkylation reaction of step a, but those hydroxy functionalities present in the piperidine compounds of structure (68), wherein R_1 is hydroxy may be protected with a suitable protecting group. The selection and utilization of suitable protecting groups for the piperidine compounds of structure (68), wherein R_1 is hydroxy is well known by one of ordinary skill in the art and is described in "Protective Groups in Organic Syntheses", Theodora W. Greene, Wiley (1981). For example, suitable protecting groups for those hydroxy functionalities present include ethers such as tetrahydrothiopyranyl, tetrahydrothiofuranyl, 2-(phenylselenyl)ethyl ether, o-nitrobenzyl ether, trimethylsilyl ether, isopropyldimethylsilyl ether, t-butyldimethylsilyl ether, t-butyldiphenylsilyl ether, tribenzylsilyl ether, triisopropylsilyl ether; and esters, such as acetate ester, isobutyrate ester, pivaloate ester, adamantate ester, benzoate ester, 2,4,6-trimethylbenzoate (mesitoate) ester, methyl carbonate, p-nitrophenyl carbonate, p-nitrobenzyl carbonate, S-benzyl thiocarbonate and N-phenylcarbamate.

The piperidine compounds of structure (68) are readily available to one of ordinary skill in the art and are described in United States Patent No. 4,254,129, March 3, 1981, United States Patent No. 4,254,130, March 3, 1981, United States Patent No. 4,285,958, April 25, 1981 and United States Patent No. 4,550,116, Oct. 29, 1985. The piperidine compounds of structure (68) wherein R_1 and R_2 form a second bond between the carbon atoms bearing R_1 and R_2 may be prepared by dehydration of the corresponding compound wherein R_1 is hydroxy by procedures generally known in the art, such as refluxing in strongly acidic solution.

The piperidine compounds of structure (68) include the limitations provided for previously for piperidine derivatives of formula (I) and (XI) in that when R_1 and R_2

are taken together to form a second bond between the carbon atoms bearing R_1 and R_2 or where R_1 represented hydroxy, m is an integer 0.

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In step b, the ω' -halo functionality of the appropriate ω -halo- α' -hydroxy- α,α -dimethylphenyl compound of structure (70) wherein R_5 is hydrogen, CN, COOalkyl or CONR₆R₇ is alkylated with the appropriate piperidine compound of structure (68) to give the corresponding ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl compound of structure (71) wherein R_5 is hydrogen, CN, COOalkyl or CONR₆R₇ as described previously in step a.

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In step c, the ketone functionality of the appropriate ω' -piperidine- α' -keto- α,α -dimethylphenyl compound of structure (69) wherein R_5 is hydrogen, CN, COOalkyl or CONR₆R₇ is reduced to give the corresponding ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl compound of structure (71) wherein R_5 is hydrogen, CN, COOalkyl or CONR₆R₇.

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For example, reduction of the appropriate ω' -piperidine- α' -keto- α,α -dimethylphenyl compound of structure (69) wherein R_5 is hydrogen, CN, COOalkyl or CONR₆R₇, using, for example, a suitable reducing agent such as sodium borohydride, potassium borohydride, sodium cyanoborohydride, or tetramethylammonium borohydride is carried out in lower alcohol solvents, such as, methanol, ethanol, isopropyl alcohol or n-butanol at temperatures ranging from about 0°C to the reflux temperature of the solvent, and the reaction time varies from about 1/2 hour to 8 hours. Other suitable reducing agents are, for example, lithium tri-tert-butylaluminumhydride and diisobutylaluminum hydride. These reduction reactions are carried out in suitable solvents diethyl ether, tetrahydrofuran or dioxane at temperatures ranging from about 0°C to the reflux temperature of the solvent, and the reaction time varies from about 1/2 hour to 8 hours.

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Catalytic reduction may also be employed in the preparation of appropriate ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl compound of structure (71) wherein R_5 is hydrogen, CN, COOalkyl or CONR₆R₇ from an appropriate ω' -piperidine- α' -keto- α,α -dimethylphenyl compound of structure (69) wherein R_5 is hydrogen, CN, COOalkyl or CONR₆R₇, using hydrogen gas in the presence of a suitable catalyst such as Raney nickel, palladium, platinum or rhodium catalysts in lower alcohol solvents, such as, methanol, ethanol, isopropyl alcohol or n-butanol or acetic acid or their aqueous mixtures, or by the use of aluminum isopropoxide in isopropyl alcohol.

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Reduction using sodium borohydride or potassium borohydride is preferred over catalytic reduction for those ω' -piperidine- α' -keto- α,α -dimethylphenyl compound of structure (69) wherein R_5 is hydrogen, CN, COOalkyl or CONR₆R₇ and wherein R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 .

In addition, a chiral reduction of the appropriate ω' -piperidine- α' -keto- α,α -dimethylphenyl compound of structure (69) wherein R_5 is hydrogen, CN, COOalkyl or CONR₆R₇, using, for example, (+)-B-chlorodiisopinocampheylborane gives the corresponding (R)- ω' -piperidine- α' -keto- α,α -dimethylphenyl compound of structure (69) wherein R_5 is hydrogen, CN, COOalkyl or CONR₆R₇ and (-)-B-chlorodiisopinocampheylborane gives the corresponding (S)- ω' -piperidine- α' -keto- α,α -dimethylphenyl compound of structure (69) wherein R_5 is hydrogen, CN, COOalkyl or CONR₆R₇. Other suitable chiral reducing agents are, (R) and (S)-oxazaborolidine/BH₃, potassium 9-O-(1,2:5,6-di-O-isopropylidene- α -D-glucofuransoyl)-9-boratabicyclo[3.3.1]nonane, (R) and (S)-B-3-pinanyl-9-borabicyclo[3.3.1]nonane, NB-Enantride, Lithium (R)-(+ and (S)-(-)-2,2'-dihydroxy-1,1'-binaphthylalkoxyl aluminum hydride, (R)-(+ and (S)-(-)-2,2'-

dihydroxy-6,6'-dimethylbiphenyl borane-amine complex,
tris[[(1S,2S,5R)-2-isopropyl-5-methyl-cyclohex-1-
yl)methyl]aluminum, [[(1R,3R)-2,2-

- 5 dimethylbicyclo[2.2.1]hept-3-yl)methyl]beryllium chloride,
(R)-BINAP-ruthenium complex/H₂ and 6,6'-
bis(diphenylphosphino)-3,3'-dimethoxy-2,2',4,4'-
tetramethyl-1,1'-biphenyl.

- 10 Starting materials for use in Scheme L are readily
available to one of ordinary skill in the art.

The following examples present typical syntheses as
described in Scheme K. These examples are understood to be
15 illustrative only and are not intended to limit the scope
of the present invention in any way. As used herein, the
following terms have the indicated meanings: "g" refers to
grams; "mmol" refers to millimoles; "mL" refers to
milliliters; "bp" refers to boiling point; "°C" refers to
20 degrees Celsius; "mm Hg" refers to millimeters of mercury;
"μL" refers to microliters; "μg" refers to micrograms; and
"μM" refers to micromolar.

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Example 43

- Step a: 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]- α,α -dimethylbenzeneacetic acid methyl ester
- 5 Mix methyl 4'-(4-chloro-1-oxobutyl)- α,α -dimethylbenzene acetate (0.335mol), α,α -diphenyl-4-piperidinemethanol (101.8g, 0.335mol), potassium hydrogen carbonate (83.8g, 0.838mol), potassium iodide (1.00g, 0.006mol), toluene
- 10 (600mL) and water (220mL). Stir at reflux for 72 hours, add toluene (200mL) and deionized water (100mL). Filter through filter aid while at 80°C and separate the organic phase. Dry (MgSO₄), filter and purify by chromatography to give the title compound.

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Example 44

- Step a: 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]- α,α -dimethylbenzeneacetic acid ethyl ester
- 20 Method A: Remove the still head from the reaction flask containing a solution of ethyl 4'-(4-chloro-1-oxobutyl)- α,α -dimethylbenzene acetate and xylenes obtained from Example 11, Method G and reattach a reflux condenser. At ambient temperature, add azacyclonol free base which has
- 25 been recrystallized from toluene (178.28g, 0.660mol) and stir at 175 RPM while heating by heating mantle. After the temperature of the reaction slurry reaches 137 (approximately 30 minutes), stir the reaction for 5.5 hours, maintaining the temperature between 137-144C.
- 30 Remove the heating mantle, add mixed xylenes (100mL) and allow the reaction slurry to cool to 64C. Increase the stirring rate to 300 RPM and add glacial acetic acid (15.17g, 0.253mol). Maintain the temperature at 64-69C for 1.9 hours by heating with mantle, cool from 64-60C over a
- 35 period of 15 minutes; and from 60-50C over a period of 32 minutes; from 50-42C over a period of 33 minutes. Filter at 42C by suction through a 350 mL coarse sintered glass filter funnel and wash the filtercake with mixed xylenes

(200mL) at ambient temperature. Allow the filtrate to stand at ambient temperature overnight then place in a 1L flask. Add isopropanol (40mL) and attached an overhead paddle stirrer. With stirring at 150 RPM, slowly add 37% aqueous concentrated HCl at ambient temperature, adding 2.00g during the first 17 minutes, adding a total of 33.13 g of HCl over 245 minutes. After the slurry has been digested, collect the solids by suction filtration through a 350mL coarse sintered glass funnel and wash the filtercake with fresh xylenes (200mL) and then with n-heptane (100mL). Dry the filtercake under vacuum at 47C for 2.5 days to give the title compound as an off-white solid (141.17g, 81%).

Concentrate the filtrate by rotary evaporator to give a thick residue of solids and syrup (23.78g). Add acetone (68g) and agitate by swirling until the syrup dissolves or releases as a solid. Collect the solids by suction filtration through a medium sintered glass funnel, wash with fresh acetone (17g) and dry under vacuum to give the title compound as a light tan solid (3.75g).

Method B: Place the solution of ethyl 4'-(4-chloro-1-oxobutyl)- α,α -dimethylbenzene acetate and xylenes obtained from Example 11, Method G in a 1L, 3-neck round bottom flask and add azacyclonol free base recrystallied from toluene (192.2g, 0.719mol). Stir the resulting slurry by overhead stirrer and heat to 140C for 5.5 hours. Allow to cool to ambient temperature and add a mixture of 4-[4-(4-(hydroxydiphenylmethyl)-1-piperidinyl)-1-oxobutyl]- α,α -dimethylbenzeneacetic acid ethyl ester hydrochloride (33.8g, 0.0318 mol) and azacyclonol hydrochloride (0.0534mol), slurried in mixed xylenes (100mL). Reheat the resulting slurry to 135C with stirring and then allow to cool slowly to ambient temperature.

-160-

Vacuum filter and wash the filtercake with xylenes. Dry the filtercake under vacuum to give a solid (122.4g). Concentrate the filtrate by rotary evaporator to a weight of 486g and add, by dropwise addition, 91g (2.75g, 0.0753mol) of a solution of HCl gas (5.6g) in absolute 2B ethanol (180mL) at 70-80C over a 1.5 hour period. Cool slowly to 30C and filter by vacuum. Wash the filtercake with mixed xylenes and dry under vacuum at 50C to give the title compound as a solid (49.1g).

To the filtrate from the second filtercake, add absolute 2B ethanol (100mL), heat to 50C and sparge gaseous HCl (about 5g) into the solution. Add additional mixed xylenes (170mL) and absolute 2B ethanol (100mL) and heat to 70C. Sparge in additional HCl gas until the total HCl added is 10g (0.274mol). Cool to 50C and stir for 2 hours then cool to ambient temperature and stir overnight.

Distill a total of 240mL of ethanol and xylenes from the slurry under reduced pressure (80mm, with pot temperature from 50 to 70C). Cool to 30C over a 1 hour period and filter by vacuum. Wash the filtercake with toluene and dry under vacuum at 50C to give the title compound as a solid (119.2g).

Method C: Place ethyl 4'-(4-chloro-1-oxobutyl)- α,α -dimethylbenzene acetate (15.00g, 49.53mmol), azacyclonol free base (29.66g, 49.53mmol) and mixed xylenes (60mL) in a 250mL 1-neck round bottom flask fitted with a magnetic stir bar and reflux condenser. Heat the reaction mixture to reflux over a period of 15 minutes and then continue at reflux for 5.5 hours. Cool to ambient temperature and then to ice/water bath temperature. Separate the solids from the orange xylenes solution by suction filtration through a coarse sintered glass funnel, wash the filtercake with cold xylenes (25mL) and dry in a vacuum oven at 60C to give the title compound as an off-white solid (16.21g).

-161-

- Method D: Place azacyclonol free base (35.00g, 125.68mmol), ethyl 4'-(4-chloro-1-oxobutyl)- α,α -dimethylbenzene acetate (17.30g, 57.13mmol) and mixed xylenes (60mL) into a 250mL round bottom flask. Heat to reflux by mantel in 13 minutes and stir by magnetic bar and heat at reflux for 6.3 hours. Remove the heat from the reaction flask and cool by ice/water bath. Filter the cold reaction slurry by suction through a coarse sintered glass funnel and wash the filtercake with fresh mixed xylenes (40mL). Vacuum dry the filtercake at 40C overnight to give the title compound as a solid (17.87g).
- 15 Add concentrated 37% HCl (2.18g, 22.1mmol) to the filtrate, stirred by magnetic bar. Stir overnight at ambient temperature, filter through suction through a coarse sintered glass funnel and wash the filtercake with fresh mixed xylenes (35mL). Vacuum dry the filtercake at 50C to give the title compound as a solid (8.23g).

- Add concentrated 37% HCl (6.42g, 65.2mmol) to the filtrate stirred by magnetic bar. Add mixed xylenes (70mL) and filter through a coarse sintered glass funnel, at ambient temperature. Wash the filtercake with fresh mixed xylenes (50mL) and vacuum dry the filtercake to give the title compound as a solid (27.25g).

- Purify by recrystallization as follows: Mix the title compound (15g), absolute 2B ethanol (45mL) and n-heptane (90mL) in a 500 mL round bottom flask with a magnetic stir bar. Heat at reflux with stirring for 30 minutes, cool by ice/water bath and collect the solids by suction filtration through a coarse sintered glass funnel. Wash the filtercake with 3:1 n-heptane/ethanol (24mL) and dry under vacuum at 55C to give the title compound as a white solid.

Example 45

Step c: 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid

Add sodium borohydride (0.105g, 2.77mmol) to a solution of
5 sodium hydroxide (0.053g, 1.33mmol) in deionized water
(2mL) and add, by dropwise addition, to a solution of 4-[4-
[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]- α,α -
dimethylbenzeneacetic acid hydrochloride (0.70g, 1.31mmol)
in ethanol (30mL). Stir at room temperature for 3.5 hours
10 at pH 7-8. Evaporate the solvent *in vacuo* and stir the
residue with methylene chloride (15mL) and deionized water
(15mL). Dry (MgSO₄), acidify to pH 3 with gaseous hydrogen
chloride and evaporate the solvent. Add ether with
stirring, filter the white solid and wash with additional
15 ether. Dry to give the title compound.

Example 46

Step c: (R)-4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic,
20 ethyl ester

Dissolve (+)-B-chlorodiisopinocampheylborane (2.5g,
7.8mmol) in anhydrous tetrahydrofuran (5mL). Add a
solution of 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-
1-oxobutyl]- α,α -dimethylbenzeneacetic, ethyl ester (2g,
25 3.54mmol) in anhydrous tetrahydrofuran (5mL). Stir at room
temperature for 3 days and cool to 0°C. Add water (1mL)
and 30% hydrogen peroxide (2mL) and stir for 20 minutes.
Add methylene chloride (30mL) and wash with brine (30mL),
then aqueous sodium hydrogen carbonate (30mL), then brine
30 (30mL). Dry (MgSO₄), evaporate the solvent *in vacuo* and
purify by chromatography to give the title compound.

Example 47

Step c: (S)-4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic
35 acid, ethyl ester

Dissolve (-)-B-chlorodiisopinocampheylborane (2.5g,
7.8mmol) in anhydrous tetrahydrofuran (5mL). Add a

-163-

- solution of 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]- α,α -dimethylbenzeneacetic acid, methyl ester (3.54mmol) in anhydrous tetrahydrofuran (5mL). Stir at
- 5 room temperature for 3 days and cool to 0°C. Add water (1mL) and 30% hydrogen peroxide (2mL) and stir for 20 minutes. Add methylene chloride (30mL) and wash with brine (30mL), then aqueous sodium hydrogen carbonate (30mL), then brine (30mL). Dry (MgSO₄), evaporate the solvent *in vacuo*
- 10 and purify by chromatography to give the title compound.

Example 48

Step a: N,N-Dimethyl-2-(4-{4-[4-hydroxy-diphenylmethyl)-piperidin-1-yl]-butyryl}-phenyl)-isobutyramide

- 15 Dissolve N,N-dimethyl-2-[4-(4-chlorobutyryl)-phenyl]-isobutyramide (1.00g, 3.38mmol) in xylene (3mL) and add α,α -diphenyl-4-piperidinemethanol (1.09g, 4.07mmol) and potassium hydrogen carbonate (0.68g, 6.76mmol) in water (2.5mL). Heat at 100°C for 20 hours, remove hot water by
- 20 pipette, dilute with ethyl acetate (20mL) and wash with water (20mL). Cool the organic layer to room temperature, dry (MgSO₄), evaporate the solvent *in vacuo* and purify by silica gel chromatography (9:1 ethyl acetate/methanol) and recrystallize (ethyl acetate/hexane) to give the title
- 25 compound (1.13g, 63%) as a crystalline solid; mp 135-137°C.

Example 49

Step c: N,N-Dimethyl-2-(4-{1-hydroxy-4-[4-hydroxy-diphenylmethyl)-piperidin-1-yl]-butyryl}-phenyl)-isobutyramide

- 30 Dissolve N,N-dimethyl-2-(4-{4-[4-hydroxy-diphenylmethyl)-piperidin-1-yl]-butyryl}-phenyl)-isobutyramide (3.00g, 5.69mmol) in ethanol (30mL), cool using an ice/water bath and add sodium borohydride (0.87g, 23.04mmol) in
- 35 tetrahydrofuran (10mL). Remove the cold bath and stir at room temperature for 2.5 hours. Add water (25mL) and ethyl acetate (25mL) and separate the layers. Extract the aqueous layer with ethyl acetate (20mL), dry (MgSO₄) and

-164-

evaporate the solvent *in vacuo* to give the title compound (3.06g, 100%) as a white foam; mp 166-169°C.

5 MS (CI, CH₄) m/e 529 (M⁺+1), 280, 183.

Anal. Calcd for C₃₄H₄₄N₂O₃•0.3H₂O: C, 77.24; H, 8.39; N, 5.30; Found: C, 76.99; H, 8.36; N, 5.17.

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Example 50

Step a: N-Methoxy-N-methyl-2-(4-{4-[4-hydroxy-diphenylmethyl]-piperidin-1-yl}-butyryl)-phenyl)-isobutyramide

Dissolve N-methoxy-N-methyl-2-[4-(4-chlorobutyryl)-phenyl]-
15 isobutyramide (1.44g, 4.62mmol) in 2:1 xylene/water (5mL) and add α,α-diphenyl-4-piperidinemethanol (1.36g, 5.07mmol) and potassium hydrogen carbonate (0.93g, 9.24mmol). Heat at 108°C for 22 hours, remove hot water by pipette, cool to room temperature and stir for 2 days. Evaporate the
20 solvent *in vacuo* and purify by silica gel chromatography (10:1 ethyl acetate/methanol) and recrystallize (ethyl acetate) to give the title compound (1.77g, 71%) as a white crystalline solid; mp 159-160.5°C.

25 MS (CI, CH₄) m/e 543 (M⁺+1), 293, 250, 183.

Anal. Calcd for C₃₄H₄₂N₂O₄•0.3H₂O: C, 74.50; H, 7.83; N, 5.11; Found: C, 74.75; H, 7.96; N, 5.15.

30

Example 51

Step c: N-Methoxy-N-methyl-2-(4-{1-hydroxy-4-[4-hydroxy-diphenylmethyl]-piperidine-1-yl}-butyryl)-phenyl)-isobutyramide

Dissolve N-methoxy-N-methyl-2-(4-{4-[4-hydroxy-diphenylmethyl]-piperidin-1-yl}-butyryl)-phenyl)-
35 isobutyramide (8.83g, 16.27mmol) in 3.5:1 methanol/tetrahydrofuran (85mL). Add sodium borohydride (0.62g, 16.27mmol) in 8 portions over 20 minutes at room

-165-

temperature. Stir at room temperature for 2 hours, evaporate the solvent *in vacuo*, dissolve the residue in ethyl acetate (60mL) and add water (25m). Stir at room temperature for 10 minutes, separate the layers and wash the organic layer with brine (2X25mL). Combine the organic layers, extract with ethyl acetate (35mL), dry (Na_2SO_4), evaporate the solvent *in vacuo* and dry to give the title compound (8.89g, 100%) as a foam; mp 80-83°C.

MS (CI, CH_4) m/e 545 ($\text{M}^+ + 1$), 280, 236, 183.

Anal. Calcd for $\text{C}_{34}\text{H}_{44}\text{N}_2\text{O}_4 \cdot 0.2\text{H}_2\text{O}$: C, 74.47; H, 8.16; N, 5.12; Found: C, 74.08; H, 8.16; N, 4.93.

Example 52

Step a: 1-[4-(1,1-Dimethyl-2-oxo-2-pyrrolidin-1-yl-ethyl)-phenyl]-4-[4-hydroxy-diphenylmethyl]-piperidine-1-yl]-butan-1-one

- 20 Dissolve 4-chloro-1-[4-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-yl-ethyl)-phenyl]-butan-1-one (6.88g, 21.38mmol) in xylene (14mL) and add a suspension of α, α -diphenyl-4-piperidinemethanol hydrochloride (6.50g, 23.51mmol) and potassium carbonate (6.14g, 4.44mmol) in water (30mL).
- 25 Heat at 100°C for 24 hours, cool to room temperature, add methylene chloride (100mL) and separate the layers. Extract the aqueous layer with methylene chloride (100mL), wash with water (150mL), dry (Na_2SO_4), evaporate the solvent *in vacuo* and purify by silica gel chromatography (4:1 ethyl acetate/methanol) to give the title compound (8.20g, 70%) as an off-white solid.
- 30

Anal. Calcd for $\text{C}_{36}\text{H}_{44}\text{N}_2\text{O}_3 \cdot 2\text{H}_2\text{O}$: C, 77.72; H, 8.04; N, 5.08; Found: C, 77.38; H, 7.91; N, 4.93.

Example 53

Step c: 2-(4-(1-Hydroxy-4-[4-hydroxydiphenylmethyl])-

piperidin-1-yl]-butyl]-phenyl)-2-methyl-1-pyrrolidin-1-yl-
propan-1-one

Dissolve 1-[4-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-yl-ethyl)-
5 phenyl]-4-[4-hydroxy-diphenylmethyl)-piperidine-1-yl]-
butan-1-one (0.55g, 1.00mmol) in methanol (10mL) and add
sodium borohydride (38mg, 1.00mmol) at 10°C. Stir at room
temperature for 2 hours, evaporate the solvent *in vacuo* and
dissolve the residue in methylene chloride (60mL). Add
10 water (10mL) and stir for 10 minutes. Separate the layers,
wash with brine (5mL), dry (Na₂SO₄) and evaporate the
solvent *in vacuo* to give the title compound (0.53g, 96%) as a
white foam; mp 87-93°C.

15

Example 54

Step a: 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-
oxobutyl]- α,α -dimethylbenzeneacetic acid, ethyl ester
hydrochloride

Dissolve 2-[4-(4-chloro-butyryl)-phenyl]-2-methyl-propionic
20 acid, ethyl ester (15.0g, 49.53mmol) and α,α -diphenyl-4-
piperidinemethanol (29.66g, 106.4mmol) in xylene (60mL).
Reflux for 5.5 hours, cool in an ice bath, filter and wash
with cold xylenes (25mL). Filter the filtrate through
silica gel (20g) and wash the gel with xylenes (40mL). Add
25 xylene (60mL) and concentrated hydrochloric acid (6.45g,
65.6mmol) with stirring. Add additional xylenes (40mL) and
stir for 2 hour. Filter, wash with xylene (50mL), vacuum
dry and slurry with a mixture of ethanol (60mL) and hexane
(120mL) at 70-72°C for 30 minutes. Filter, wash with 3:1
30 v/v solution of n-heptane/ethanol (30mL) and dry to give
the title compound as a light white solid (19.7g, 70%); mp
206-208°C.

¹H NMR (300MHz, CDCl₃) δ 7.90 (d, J=8.7Hz, 2H), 7.47 (m,
35 4H), 7.41 (d, J=8.7Hz, 2H), 7.27 (m, 4H), 7.15 (m, 4H),
4.10 (q, J=7.1Hz, 2H), 2.93 (m, 4H), 2.37 (m, 3H), 2.2
(broad s, 1H), 1.92 (m, 4H), 1.59 (s, 6H), 1.39 (m, 4H),
1.16 (t, J=7.1Hz, 3H); ¹³C NMR (75MHz, CDCl₃) δ 199.5,

-167-

176.1, 149.8, 146.0, 135.5, 128.2, 128.1, 126.4, 125.9,
125.7, 79.4, 61.0, 57.8, 53.9, 46.7, 44.1, 36.3, 26.3,
26.2, 21.9, 14.0; IR (CDCl₃) 3514, 2945, 1726, 1682, 1446,
5 1254, 1147 1097 cm⁻¹;

Anal. Calcd for C₃₄H₄₁O₄N•HCl: C, 72.39; H, 7.50; N, 2.48;
Found: C, 71.68; H, 7.52; N, 2.34.

10

Example 55

Step a: 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]-α,α-dimethylbenzeneacetic acid, methyl ester hydrochloride

Dissolve 2-[4-(4-chloro-butyryl)-phenyl]-2-methyl-propionic
15 acid, methyl ester (2.82g, 10.0mmol) and α,α-diphenyl-4-piperidinemethanol (5.58g, 21.0mmol) in toluene (20mL). Reflux for 29 hours, cool in an ice bath, filter, filter the filtrate through silica gel (5g) and wash the gel with toluene (10mL). Evaporate the solvent *in vacuo* and dissolve
20 the residue in ethyl ether (100mL). Add anhydrous hydrogen chloride and filter to give the title compound as an off-white powder (4.2g, 76%); mp 165-175°C.

¹H NMR (300MHz, CDCl₃) δ 7.93 (d, J=8.3Hz, 2H), 7.47 (m, 4H), 7.42 (d, J=8.3Hz, 2H), 7.30 (m, 4H), 7.18 (m, 2H), 3.64 (s, 3H), 2.96 (m, 4H), 2.42 (m, 4H), 1.96 (m, 4H), 1.62 (s, 6H), 1.41 (m, 4H); ¹³C NMR (75MHz, CDCl₃) δ 199.1, 176.3, 149.4, 145.8, 135.5, 128.1, 128.0, 127.7, 126.3, 125.7, 1225.6, 79.4, 57.9, 54.0, 52.4, 46.9, 44.1, 36.4,
30 26.4, 26.3, 22; MS (CI/NH₃) 514 (100 (M+H)), 293 (4), 268 (7).

Anal. Calcd for C₃₃H₃₉O₄N•HCl: C, 72.05; H, 7.33; N, 2.55;
Found: C, 71.85; H, 7.23, N, 2.33.

35

Example 56

Step c: 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-

hydroxybutyl)- α,α -dimethylbenzeneacetic acid, methyl ester hydrochloride

Dissolve 4-[4-(4-(hydroxydiphenylmethyl)-1-piperidiny]-1-oxobutyl)- α,α -dimethylbenzeneacetic acid, methyl ester hydrochloride (550mg, 1.00mmol) in methanol (5mL) and add sodium borohydride (62.8mg) in three batches. Stir for 1 hour, add 50% aqueous sodium hydroxide (800mg) and heat to reflux with stirring. After 3 hours, cool to -10°C , add approximately 1.5mL of 6N HCl over 10 minutes, filter the solid and wash with ice water (12mL) such that the final filtrate is pH=5. Dry the resulting solid *in vacuo* ($50-60^{\circ}\text{C}$, 10-1 mm) overnight to give the title compound (515mg, 94%); mp $165-180^{\circ}\text{C}$.

15

^1H NMR (300MHz, 5% MeOD₄ in CDCl₃) δ 7.50 (d, $J=7.3\text{Hz}$, 4H), 7.30 (m, 8H), 7.18 (t, $J=7.0\text{Hz}$, 2H), 4.66 (t, $J=5.3\text{Hz}$, 1H), 3.47 (m, 6H), 2.97 (m, 2H), 2.69 (m, 3H), 1.6-2.2 (m, 6H), 1.55 (s, 6H); ^{13}C NMR (75MHz, 5% MeOD₄ in CDCl₃) δ 179.1, 145.3, 143.8, 142.3, 128.2, 126.6, 125.7, 125.5, 125.4, 78.4 (bis benzylic), 72.5 (benzylic), 57.4, 53.2, 46.2, 24.2, 35.9, 26.6, 24.1, 20.8; MS (CI/NH₃) 502 (100 (M+H)), 280 (5), 200 (10).

25

Example 57

Step c: 2-(4-(1-Hydroxy-4-(4-(hydroxydiphenylmethyl)-1-piperidiny)-butyl)-phenyl)-2-methyl-propanol

Dissolve 2-(4-(1-oxo-4-(4-(hydroxydiphenylmethyl)-1-piperidiny)-butyl)-phenyl)-2-methylpropanol in methanol (450mL) and stir for 15 minutes at room temperature. Add, by dropwise addition, a solution of sodium borohydride (2.25g, 0.06mol) in water (10mL) over 15 minutes. Stir for another 30 minutes and cool in an ice-bath. Slowly add concentrated hydrochloric acid (4mL) and water (8mL) and stir for an additional 20 minutes. Evaporate the solvent *in vacuo* and partition the residue between methylene chloride (150mL) and water (70mL). Separate the organic phase and

-169-

extract the aqueous phase with methylene chloride (25mL). Wash the combined organic layers with water (2X50mL), evaporate the solvent *in vacuo* and recrystallize (acetone) to
5 give the title compound as white needles (9.53g, 79%).

¹H NMR (300MHz, DMSO-d₆) δ 7.50 (4H, m), 7.23 (8H, m), 7.12 (2H, m), 5.34 (1H, s, br), 4.65 (1H, t), 4.45 (1H, s), 3.38 (2H, t), 2.60 (2H, m), 2.44 (2H, m), 2.20 (2H, t), 1.62
10 (2H, t), 1.50 (6H, m), 1.98 (6H, s); ¹³C NMR (DMSO-d₆) δ 147.2, 146.0, 143.4, 127.6, 125.6, 125.5, 125.2, 78.4, 72.0, 70.9, 58.0, 53.6, 53.5, 43.6, 38.0, 30.5, 25.9, 25.5, 23.1.

15

Alternatively, the novel intermediates of formula (XI) may be prepared as described in Scheme M. In Scheme M, all substituents are as previously defined unless otherwise indicated.

20

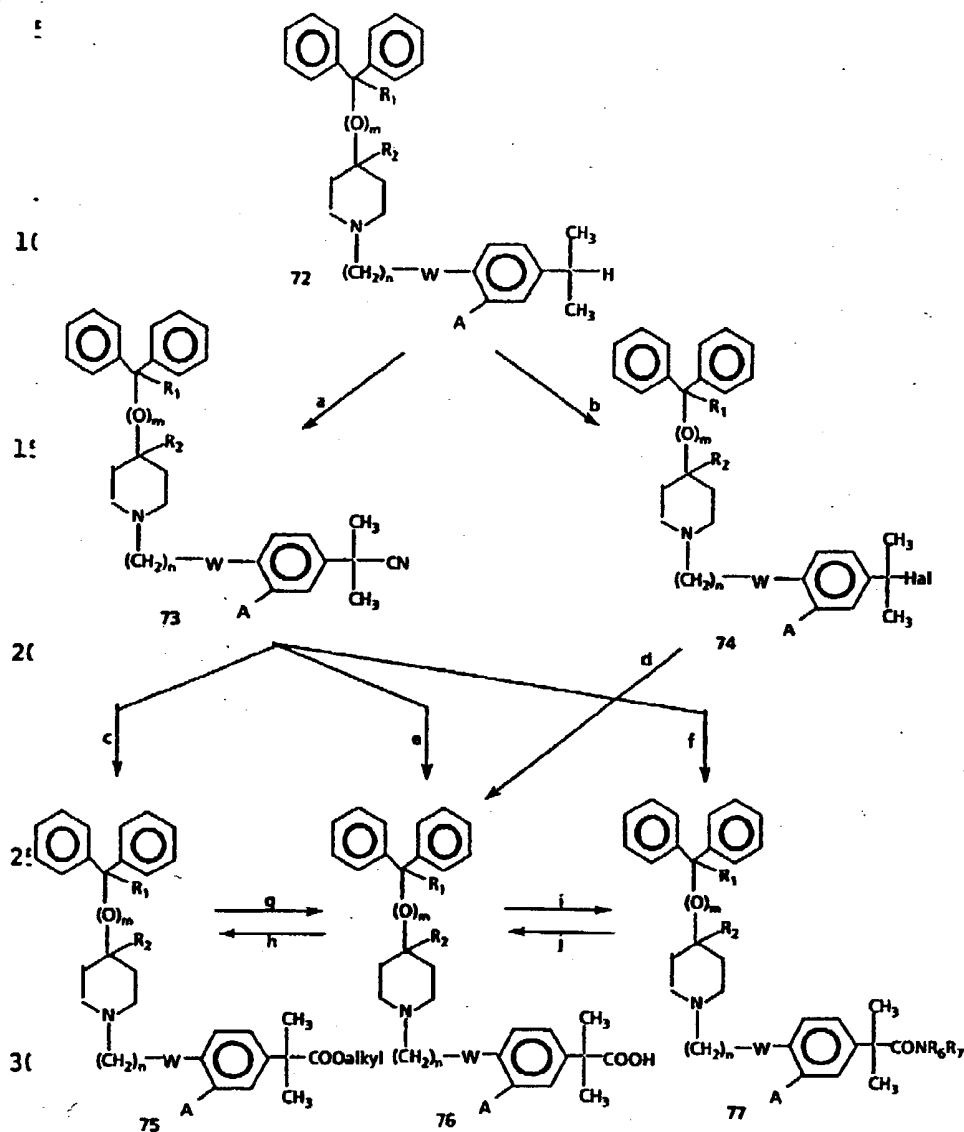
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-170-

Scheme M



W = -C(=O)- or -CH(OH)-

35

Scheme M provides various alternative general synthetic procedures for preparing the novel intermediates of formula (XI).

-171-

In step a, the appropriate ω' -piperidine-2-methylethylphenyl compound of structure (72) is cyanated to
5 give the corresponding ω' -piperidine- α,α -dimethylphenylacetonitrile compound of structure (73) as described previously in Scheme D, step b.

In step b, the appropriate ω' -piperidine-2-methylethylphenyl compound of structure (72) is halogenated
10 to give the corresponding ω' -piperidine- α,α -dimethylbenzyl halide compound of structure (74) as described previously in Scheme B, step a.

In step c, the nitrile functionality of the appropriate ω' -piperidine- α,α -dimethylphenylacetonitrile
15 compound of structure (73) is converted to the corresponding ester to give the ω' -piperidine- α,α -dimethylphenylacetic acid ester compound of structure (75)
20 as described previously in Scheme H, step a.

In step d, the halo functionality of the appropriate ω' -piperidine- α,α -dimethylbenzyl halide compound of
structure (74) is converted to the corresponding carboxy to
25 give the ω' -piperidine- α,α -dimethylphenylacetic acid compound of structure (76) as described previously in Scheme H, step h.

In step e, the nitrile functionality of the appropriate ω' -piperidine- α,α -dimethylphenylacetonitrile
30 compound of structure (73) is converted to the corresponding carboxy to give the ω' -piperidine- α,α -dimethylphenylacetic acid compound of structure (76) as described previously in Scheme H, step e.

35
In step f, the nitrile functionality of the appropriate ω' -piperidine- α,α -dimethylphenylacetonitrile compound of structure (73) is converted to the

corresponding amide to give the ω' -piperidine- α,α -dimethylphenylacetic acid amide compound of structure (77) wherein R_6 and R_7 are each hydrogen as described previously in Scheme H, step b.

In step g, the carboxy ester functionality of the appropriate ω' -piperidine- α,α -dimethylphenylacetic acid ester compound of structure (75) is hydrolyzed to give the corresponding ω' -piperidine- α,α -dimethylphenylacetic acid compound of structure (76) as described previously in Scheme H, step c.

In step h, the carboxy functionality of the appropriate ω' -piperidine- α,α -dimethylphenylacetic acid compound of structure (76) may be esterified by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding ω' -piperidine- α,α -dimethylphenylacetic acid ester compound of structure (75) as described previously in Scheme H, step d.

In step i, the carboxy functionality of the appropriate ω' -piperidine- α,α -dimethylphenylacetic acid compound of structure (76) may be amidated by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding ω' -piperidine- α,α -dimethylphenylacetic acid amide compound of structure (77) as described previously in Scheme H, step g.

In step j, the amide functionality of the appropriate ω' -piperidine- α,α -dimethylphenylacetic acid amide compound of structure (77) is converted to the corresponding acid by acid hydrolysis as is known in the art to give the ω' -piperidine- α,α -dimethylphenylacetic acid compound of structure (76) as described previously in Scheme H, step f.

Starting materials for use in Scheme M are readily available to one of ordinary skill in the art.

The following examples present typical syntheses as described in Scheme M. These examples are understood to be illustrative only and are not intended to limit the scope of the present invention in any way. As used herein, the following terms have the indicated meanings: "g" refers to grams; "mmol" refers to millimoles; "mL" refers to milliliters; "bp" refers to boiling point; "°C" refers to degrees Celsius; "mm Hg" refers to millimeters of mercury; "μL" refers to microliters; "μg" refers to micrograms; and "μM" refers to micromolar.

Example 58

Step q: 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]-α,α-dimethylbenzeneacetic acid hydrochloride
Dissolve 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]-α,α-dimethylbenzeneacetic acid methyl ester (0.131mol) in methanol (2.5L) and add 10% sodium hydroxide (769mL, 1.92mol). Stir at reflux for 1.5 hours, cool to 68°C and evaporate the solvent *in vacuo* to a residue. Add chloroform (1L) and stir until the solids are dissolved. Separate the organic phase and extract the aqueous phase with chloroform (3X300mL). Combine the organic phases, dry (MgSO₄) and evaporate the solvent *in vacuo* to give a residue. Treat the residue with ethereal HCl, filter and dry to give the title compound.

Example 59

Step j: 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]-α,α-dimethylbenzeneacetic acid
Dissolve N-methoxy-N-methyl-2-(4-{1-hydroxy-4-[4-hydroxydiphenylmethyl)-piperidine-1-yl]-butyryl}-phenyl)-isobutyramide (8.35g, 15.33mmol) in isopropanol (50mL) and add potassium hydroxide (8.63g, 153.7mmol). Heat to reflux for 2 hours, add additional potassium hydroxide (4.35g, 77.5mmol) and heat at reflux for an additional 16 hours. Cool to room temperature, treat with concentrated HCl by

-174-

dropwise addition until pH = 3. Dilute with water (100mL), stir vigorously for 2 hours, add ethyl acetate (30mL) and stir for 1 hour. Filter to give the title compound (7.15g, 5 87%) as an off-white solid.

MS (CI, CH₄) m/e 502 (M⁺+1), 107.

Anal. Calcd for C₃₂H₃₉NO₄•HCl•2.6H₂O: C, 65.70; H, 7.61; N, 10 2.39; Found: C, 65.25; H, 7.70; N, 2.36.

Example 60

Step j: 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]-α,α-dimethylbenzeneacetic acid

15 Dissolve N,N-dimethyl-2-(4-{1-hydroxy-4-[4-hydroxy-diphenylmethyl)-piperidin-1-yl]-butyryl)-phenyl)-isobutyramide (15.33mmol) in isopropanol (50mL) and add potassium hydroxide (8.63g, 153.7mmol). Heat to reflux for 2 hours, add additional potassium hydroxide (4.35g, 20 77.5mmol) and heat at reflux for an additional 16 hours. Cool to room temperature, treat with concentrated HCl by dropwise addition until pH = 3. Dilute with water (100mL), stir vigorously for 2 hours, add ethyl acetate (30mL) and stir for 1 hour. Filter to give the title compound (41%).

25

As one skilled in the art would appreciate, the compounds depicted in Schemes A through M which bear hydroxy or phenolic functionalities may be protected prior to use in the synthesis depicted in Schemes A through M. 30 using suitable protecting groups. For example, suitable protecting groups for the phenolic hydroxy include methyl ether, 2-methoxyethoxymethyl ether (MEM), cyclohexyl ether, o-nitrobenzyl ether, 9-anthryl ether, t-butyldimethylsilyl ether, acetate, benzoate, methyl carbamate, benzyl 35 carbamate, aryl pivaloate and aryl methanesulfonate.

As one skilled in the art would appreciate, the compounds depicted in Schemes A through M which bear α-

ketone functionalities may be protected prior to use in the synthesis depicted in Schemes A through M using suitable protecting groups. The selection and utilization of

5 suitable protecting groups for ketone groups is well known by one of ordinary skill in the art and is described in "Protective Groups in Organic Syntheses", Theodora W. Greene, Wiley (1981). For example, suitable protecting groups for ketone functionalities include acyclic acetals

10 and ketals such as dimethyl acetal, cyclic acetals and ketals such as 1,3-dioxanes and 1,3-dioxolanes, dithio acetals and ketals such as 1,3-dithiane and 1,3-dithiolane, hemithio acetals and ketals, O-substituted cyanohydrins, substituted hydrozones, imines, oxazolidines,

15 imidazolidines and thiazolidines.

As one skilled in the art would appreciate, the compounds depicted in Schemes A through M which bear protected hydroxy and/or ketone functionalities may be

20 reacting with appropriate deprotecting agents prior to use in any of the steps depicted in Schemes A through M. The selection and utilization of appropriate deprotecting reagents is well known by one of ordinary skill in the art and is described in "Protective Groups in Organic

25 Syntheses", Theodora W. Greene, Wiley (1981). Examples of appropriate deprotecting reagents are mineral acids, strong organic acids, Lewis acids, aqueous mineral bases, catalytic hydrogenation and the like.

30 For example, cleavage of β -methoxyethoxymethyl (MEM) protecting groups on any of the compounds depicted in Schemes A through M which bear protected hydroxy ketone functionalities, for example, can be achieved by using trifluoroacetic acid at room temperature or using 5 to 8

35 equivalents of powdered anhydrous zinc bromide in methylene chloride at about 25°C by the general procedure of E. J. Corey et al., *Tetrahedron Letters*, 11, 809-812 1976.

In addition, the individual (R) and (S) isomers of the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl compounds of structure (71) can be prepared by techniques and procedures well known and appreciated by one of ordinary skill in the art.

For example, the mixture of (R) and (S) isomers of the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl compounds of structure (71) may be subjected to chiral chromatography to give the corresponding individual (R)- ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl compounds of structure (71) and (S)- ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl compounds of structure (71).

In addition, the individual (R) and (S) isomers of the ω -halo- α' -hydroxy- α,α -dimethylphenyl compound of structure (70) and the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl compounds of structure (71) can be prepared by techniques and procedures well known and appreciated by one of ordinary skill in the art and described in "Enantiomers, Racemates, and Resolutions", Jacques, Collet and Wilen, Wiley (1981).

One such method involves reacting the mixture of (R) and (S) isomers of the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl compounds of structure (71) with appropriate chiral acids to give the corresponding mixture of diastereomeric acid addition salts. The individual (R)- ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl chiral acid addition salt compounds of structure (71) and (S)- ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl chiral acid addition salt compounds of structure (71) are obtained by recrystallization and the individual ω' -piperidine-(R)- α' -hydroxy- α,α -dimethylphenyl compounds of structure (71) and ω' -piperidine-(S)- α' -hydroxy- α,α -dimethylphenyl compounds of structure (71) are obtained by subjecting the individual ω' -piperidine-(R)- α' -hydroxy- α,α -dimethylphenyl chiral acid

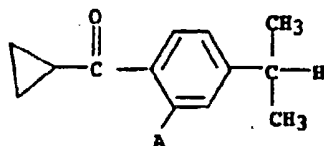
addition salt compounds of structure (71) and ω' -piperidine-(S)- α' -hydroxy- α,α -dimethylphenyl chiral acid addition salt compounds of structure (71) to base in order to free the piperidine nitrogen from the acid addition complex. Examples of suitable chiral acids are tartaric acid (+), (-), O,O'-dibenzoyltartaric acid (+), (-), O,O'-di-p-toluyltartaric acid (+), (-), 2-Nitrotartranillic acid (+), (-), mandelic acid (+), (-), malic acid (+), (-), 2-phenoxypropionic acid (+), hydratropic acid (+), (-), N-acetylleucine (-), (+), N-(α -methylbenzyl)succinamide (+), (-), N-(α -methylbenzyl)phthalamic acid (+), (-), camphor-10-sulfonic acid (+), 3-bromocamphor-9-sulfonic acid (+), (-), camphor-3-sulfonic acid (+), quinic acid (+), (-), Di-O-isopropylidene-2-oxo-L-gulonic acid (-), Lasalocid (-), 1,1'-binaphthyl-2,2'-phosphoric acid (+), (-), chloestenonesulfonic acid.

In addition, the individual (R) and (S) isomers of the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl compounds of structure (71) can be prepared by reacting the mixture of (R) and (S) isomers of the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl compounds of structure (71) with appropriate organic chiral acids to give the corresponding mixture of diastereomeric acid esters. The individual ω' -piperidine-(R)- α' -ester- α,α -dimethylphenyl compounds of structure (71) and ω' -piperidine-(S)- α' -ester- α,α -dimethylphenyl compounds of structure (71) are obtained by recrystallization or chromatography and the individual ω' -piperidine-(R)- α' -hydroxy- α,α -dimethylphenyl compounds of structure (71) and ω' -piperidine-(S)- α' -hydroxy- α,α -dimethylphenyl compounds of structure (71) are obtained by subjecting the individual ω' -piperidine-(R)- α' -ester- α,α -dimethylphenyl compounds of structure (71) and ω' -piperidine-(S)- α' -ester- α,α -dimethylphenyl compounds of structure (71) to hydrolysis conditions.

WHAT IS CLAIMED IS:

1. A compound of the formula

5

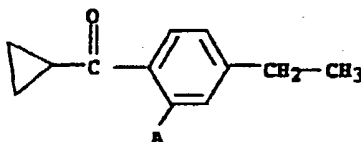


10 wherein

A is a hydrogen or hydroxy.

2. A compound of the formula

15

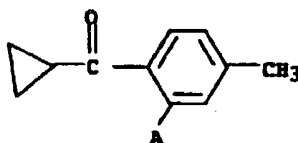


wherein

20 A is a hydrogen or hydroxy.

3. A compound of the formula

25



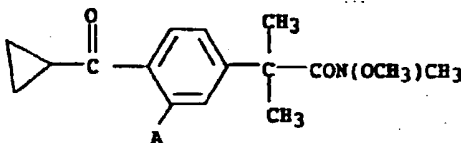
wherein

A is a hydrogen or hydroxy.

30

4. A compound of the formula

35

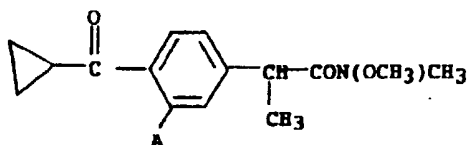


wherein

A is a hydrogen or hydroxy.

5. A compound of the formula

5

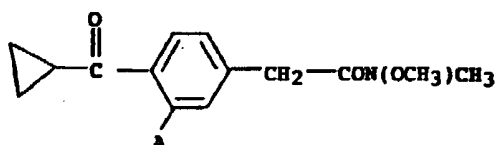


wherein

10 A is a hydrogen or hydroxy.

6. A compound of the formula

15



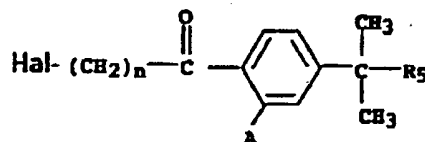
wherein

A is a hydrogen or hydroxy.

20

7. A compound of the formula

25



wherein

Hal is Cl, Br or I;

n is an integer of from 1 to 5;

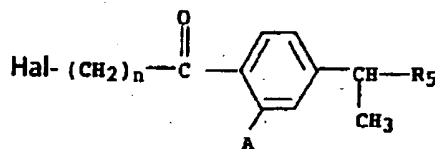
30 A is a hydrogen or hydroxy; and

R₅ is H, CH₂OD wherein D is hydrogen, acetate or benzoate, CHO, Br, Cl, I, CN, -COOH, -C(=NH)Oalkyl, or -CONR₆R₇, wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched and R₆ and R₇ are each independently H, C₁-C₆alkyl, C₁-C₆alkoxy or R₆ and R₇ taken together with the nitrogen atom form a pyrrolidine, piperidine or

35

morpholine, with the proviso that R_6 and R_7 cannot both be represented by C_1 - C_6 alkoxy.

5 8. A compound of the formula



10

wherein

Hal is Cl, Br or I;

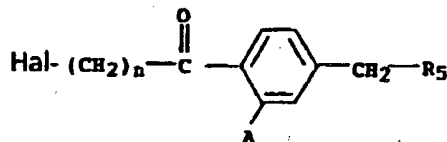
n is an integer of from 1 to 5;

A is a hydrogen or hydroxy; and

15 R_5 is H, OH, Br, Cl, I, CN, $-COOH$, $-COOalkyl$, $-C(=NH)Oalkyl$, or $-CONR_6R_7$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched and R_6 and R_7 are each independently H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy or R_6 and R_7 taken together with
20 the nitrogen atom form a pyrrolidine, piperidine or morpholine, with the proviso that R_6 and R_7 cannot both be represented by C_1 - C_6 alkoxy.

9. A compound of the formula

25



30 wherein

Hal is Cl, Br or I;

n is an integer of from 1 to 5;

A is a hydrogen or hydroxy; and

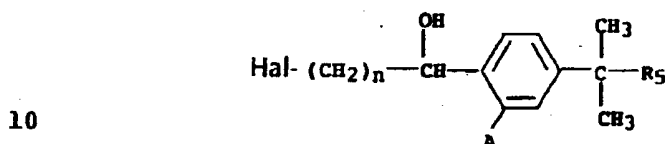
35 R_5 is H, OH, Br, Cl, I, CN, $-COOH$, $-COOalkyl$, $-C(=NH)Oalkyl$ or $-CONR_6R_7$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched and R_6 and R_7 are each independently H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy or R_6 and R_7 taken together with

-181-

the nitrogen atom form a pyrrolidine, piperidine or morpholine, with the proviso that R_6 and R_7 cannot both be represented by C_1 - C_6 alkoxy.

5

10. A compound of the formula



wherein

Hal is Cl, Br or I;

n is an integer of from 1 to 5;

15 A is a hydrogen or hydroxy; and

R_5 is H, CH_2OD wherein D is hydrogen, acetate or

benzoate, CHO, Br, Cl, I, CN, $-COOH$, $-COOalkyl$,

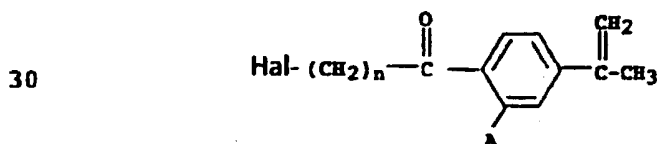
$-C(=NH)Oalkyl$ or $-CONR_6R_7$ wherein the alkyl moiety

has from 1 to 6 carbon atoms and is straight or

20 branched and R_6 and R_7 are each independently H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy or R_6 and R_7 taken together with the nitrogen atom form a pyrrolidine, piperidine or morpholine, with the proviso that R_6 and R_7 cannot both be represented by C_1 - C_6 alkoxy; and

25 individual optical isomers thereof.

11. A compound of the formula



wherein

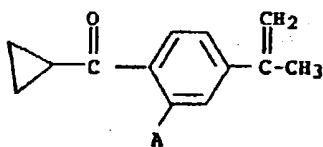
Hal is Cl, Br or I;

35 n is an integer of from 1 to 5; and

A is a hydrogen or hydroxy.

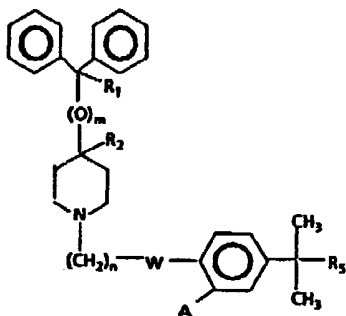
12. A compound of the formula

-182-



wherein A is a hydrogen or hydroxy.

13. A compound of the formula



20 wherein

W represents $-C(=O)-$ or $-CH(OH)-$;

R_1 represents hydrogen or hydroxy;

R_2 represents hydrogen; or

25 R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;

n is an integer of from 1 to 5;

m is an integer 0 or 1;

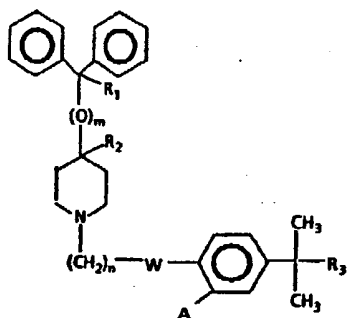
30 R_5 is H, Br, Cl, I, CN or $-CONR_6R_7$ wherein R_6 and R_7 are each independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy or R_6 and R_7 taken together with the nitrogen atom form a pyrrolidine, piperidine or morpholine, with the proviso that R_6 and R_7 cannot both be represented by C_1-C_6 alkoxy;

35 A is hydrogen or hydroxy; and pharmaceutically acceptable salts and individual optical isomers thereof, with the proviso that where R_1 and R_2 are taken together to form a second bond between the

-183-

carbon atoms bearing R_1 and R_2 or where R_1 represented hydroxy, m is an integer 0.

14. A process for preparing a compound of the formula



wherein

W represents $-C(=O)-$ or $-CH(OH)-$;

R_1 represents hydrogen or hydroxy;

R_2 represents hydrogen; or

R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;

n is an integer of from 1 to 5;

m is an integer 0 or 1;

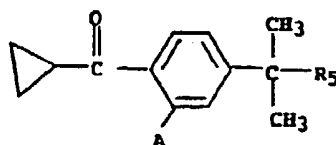
R_3 is $-COOH$ or $-COOalkyl$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;

each of A is hydrogen or hydroxy; and

pharmaceutically acceptable salts and individual optical isomers thereof, with the proviso that where R_1 and R_2

are taken together to form a second bond between the carbon atoms bearing R_1 and R_2 or where R_1 represented hydroxy, m is an integer 0

comprising using an intermediate compound of the formula



wherein

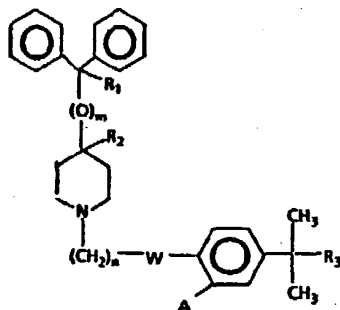
A is a hydrogen or hydroxy;

R₅ is H, -CH₂OD wherein D is hydrogen, acetate or

5 benzoate, -CHO, Br, Cl, I, CN, -COOH, -COOalkyl
or -CONR₆R₇ wherein the alkyl moiety has from 1 to 6
carbon atoms and is straight or branched and R₆ and
R₇ are each independently H, C₁-C₆alkyl, C₁-C₆alkoxy
or R₆ and R₇ taken together with the nitrogen atom
10 form a pyrrolidine, piperidine or morpholine, with
the proviso that R₆ and R₇ cannot both be
represented by C₁-C₆alkoxy.

15. A process for preparing a compound of the formula

15



20

25

wherein

W represents -C(=O)- or -CH(OH)-;

R₁ represents hydrogen or hydroxy;

R₂ represents hydrogen; or

30 R₁ and R₂ taken together form a second bond between the
carbon atoms bearing R₁ and R₂;

n is an integer of from 1 to 5;

m is an integer 0 or 1;

35 R₃ is -COOH or -COOalkyl wherein the alkyl moiety has
from 1 to 6 carbon atoms and is straight or branched;

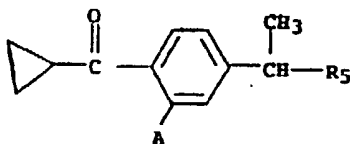
each of A is hydrogen or hydroxy; and

pharmaceutically acceptable salts and individual optical
isomers thereof, with the proviso that where R₁ and R₂

-185-

are taken together to form a second bond between the carbon atoms bearing R_1 and R_2 or where R_1 represented hydroxy, m is an integer 0,

5 comprising using an intermediate compound of the formula



10

wherein

A is a hydrogen or hydroxy; and

R_5 is H, OH, Br, Cl, I, CN, $-COOH$, $-COOalkyl$ or $-CONR_6R_7$

wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched and R_6 and

15

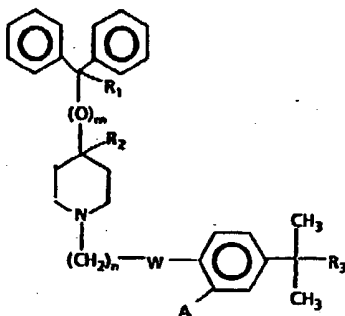
R_7 are each independently H, C_1-C_6alkyl , $C_1-C_6alkoxy$ or R_6 and R_7 taken together with the nitrogen atom form a pyrrolidine, piperidine or morpholine, with the proviso that R_6 and R_7 cannot both be

20

represented by $C_1-C_6alkoxy$.

16. A process for preparing a compound of the formula

25



30

wherein

35 W represents $-C(=O)-$ or $-CH(OH)-$;

R_1 represents hydrogen or hydroxy;

R_2 represents hydrogen; or

R₁ and R₂ taken together form a second bond between the carbon atoms bearing R₁ and R₂;

n is an integer of from 1 to 5;

5 m is an integer 0 or 1;

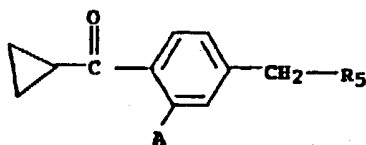
R₃ is -COOH or -COOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;

each of A is hydrogen or hydroxy; and

10 pharmaceutically acceptable salts and individual optical isomers thereof, with the proviso that where R₁ and R₂ are taken together to form a second bond between the carbon atoms bearing R₁ and R₂ or where R₁ represented hydroxy, m is an integer 0

comprising using an intermediate compound of the formula

15



20 wherein

A is a hydrogen or hydroxy; and

R₅ is H, OH, Br, Cl, I, CN, -COOH, -COOalkyl or -CONR₆R₇ wherein the alkyl moiety has from 1 to 6 carbon

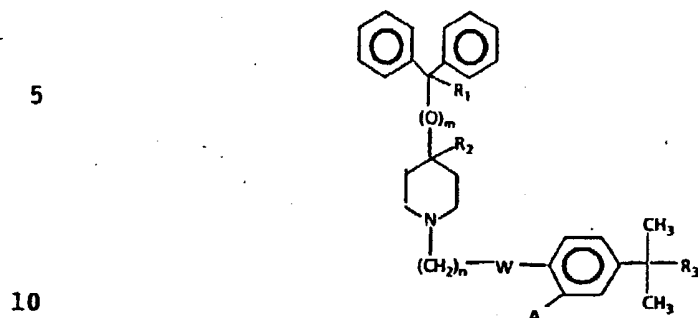
atoms and is straight or branched and R₆ and

25 R₇ are each independently H, C₁-C₆alkyl, C₁-C₆alkoxy or R₆ and R₇ taken together with the nitrogen atom form a pyrrolidine, piperidine or morpholine, with the proviso that R₆ and R₇ cannot both be represented by C₁-C₆alkoxy.

30

17. A process for preparing a compound of the formula

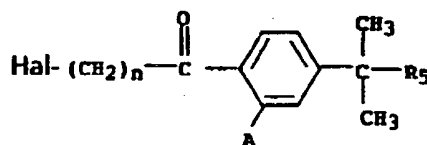
35



wherein

- W represents $-C(=O)-$ or $-CH(OH)-$;
- 15 R_1 represents hydrogen or hydroxy;
- R_2 represents hydrogen; or
- R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;
- n is an integer of from 1 to 5;
- 20 m is an integer 0 or 1;
- R_3 is $-COOH$ or $-COOalkyl$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;
- each of A is hydrogen or hydroxy; and
- pharmaceutically acceptable salts and individual optical
- 25 isomers thereof, with the proviso that where R_1 and R_2 are taken together to form a second bond between the carbon atoms bearing R_1 and R_2 or where R_1 represented hydroxy, m is an integer 0
- comprising using an intermediate compound of the formula

30

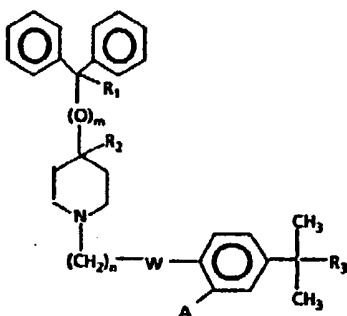


35 wherein

- Hal is Cl, Br or I;
- n is an integer of from 1 to 5;
- A is a hydrogen or hydroxy; and

R_5 is H, CH_2OD wherein D is hydrogen, acetate or benzoate, CHO, Br, Cl, I, CN, $-\text{COOH}$ or $-\text{CONR}_6\text{R}_7$ wherein R_6 and R_7 are each independently H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy or R_6 and R_7 taken together with the nitrogen atom form a pyrrolidine, piperidine or morpholine, with the proviso that R_6 and R_7 cannot both be represented by C_1 - C_6 alkoxy.

18. A process for preparing a compound of the formula



wherein

W represents $-\text{C}(=\text{O})-$ or $-\text{CH}(\text{OH})-$;

R_1 represents hydrogen or hydroxy;

R_2 represents hydrogen; or

R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;

n is an integer of from 1 to 5;

m is an integer 0 or 1;

R_3 is $-\text{COOH}$ or $-\text{COOalkyl}$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;

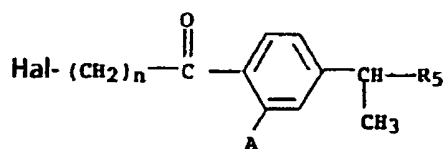
each of A is hydrogen or hydroxy; and

pharmaceutically acceptable salts and individual optical isomers thereof, with the proviso that where R_1 and R_2

are taken together to form a second bond between the carbon atoms bearing R_1 and R_2 or where R_1 represented hydroxy, m is an integer 0

comprising using an intermediate compound of the formula

-189-



5

wherein

Hal is Cl, Br or I;

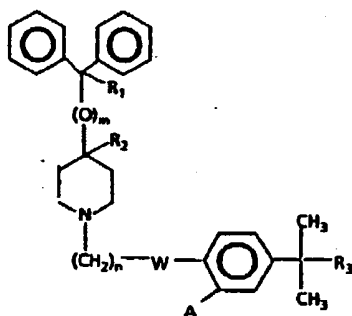
n is an integer of from 1 to 5;

10 A is a hydrogen or hydroxy; and

R₅ is H, OH, Br, Cl, I, CN, -COOH, -COOalkyl or -CONR₆R₇ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched and R₆ and R₇ are each independently H, C₁-C₆alkyl, C₁-C₆alkoxy or R₆ and R₇ taken together with the nitrogen atom form a pyrrolidine, piperidine or morpholine, with the proviso that R₆ and R₇ cannot both be represented by C₁-C₆alkoxy.

15

20 19. A process for preparing a compound of the formula



25

30

wherein

W represents -C(=O)- or -CH(OH)-;

R₁ represents hydrogen or hydroxy;35 R₂ represents hydrogen; or

R₁ and R₂ taken together form a second bond between the carbon atoms bearing R₁ and R₂;

n is an integer of from 1 to 5;

m is an integer 0 or 1;

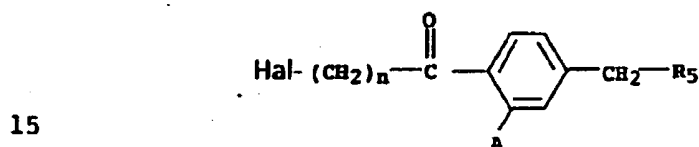
R₃ is -COOH or -COOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;

5 each of A is hydrogen or hydroxy; and

pharmaceutically acceptable salts and individual optical isomers thereof, with the proviso that where R₁ and R₂ are taken together to form a second bond between the carbon atoms bearing R₁ and R₂ or where R₁ represented

10 hydroxy, m is an integer 0

comprising using an intermediate compound of the formula



wherein

Hal is Cl, Br or I;

n is an integer of from 1 to 5;

20 A is a hydrogen or hydroxy; and

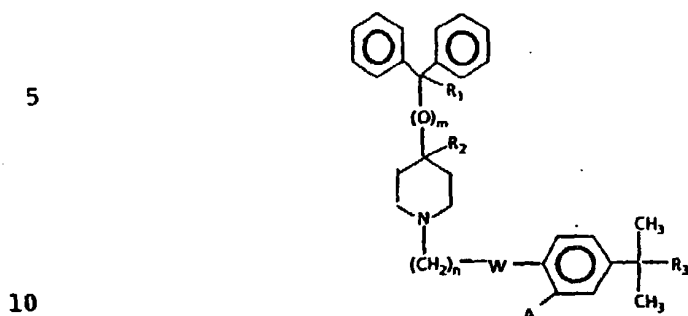
R₅ is H, OH, Br, Cl, I, CN, -COOH, -COOalkyl or -CONR₆R₇

wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched and R₆ and

R₇ are each independently H, C₁-C₆alkyl, C₁-C₆alkoxy

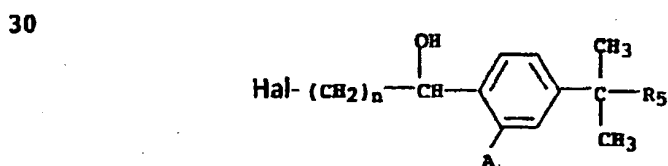
25 or R₆ and R₇ taken together with the nitrogen atom form a pyrrolidine, piperidine or morpholine, with the proviso that R₆ and R₇ cannot both be represented by C₁-C₆alkoxy.

30 20. A process for preparing a compound of the formula



wherein

- W represents $-C(=O)-$ or $-CH(OH)-$;
- 15 R_1 represents hydrogen or hydroxy;
- R_2 represents hydrogen; or
- R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;
- n is an integer of from 1 to 5;
- 20 m is an integer 0 or 1;
- R_3 is $-COOH$ or $-COOalkyl$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;
- each of A is hydrogen or hydroxy; and
- pharmaceutically acceptable salts and individual optical
- 25 isomers thereof, with the proviso that where R_1 and R_2 are taken together to form a second bond between the carbon atoms bearing R_1 and R_2 or where R_1 represented hydroxy, m is an integer 0
- comprising using an intermediate compound of the formula



35 wherein

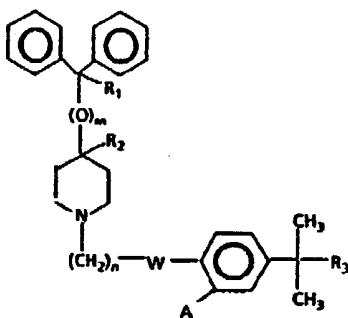
- Hal is Cl, Br or I;
- n is an integer of from 1 to 5;
- A is a hydrogen or hydroxy; and

5 R_5 is H, CH_2OD wherein D is hydrogen, acetate or benzoate, CHO, Br, Cl, I, CN, $-\text{COOH}$, $-\text{COOalkyl}$ or $-\text{CONR}_6\text{R}_7$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched and R_6 and R_7 are each independently H, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_1\text{-C}_6\text{alkoxy}$ or R_6 and R_7 taken together with the nitrogen atom form a pyrrolidine, piperidine or morpholine, with the proviso that R_6 and R_7 cannot both be
 10 represented by $\text{C}_1\text{-C}_6\text{alkoxy}$; and individual optical isomers thereof.

21. A process for preparing a compound of the formula

15

20



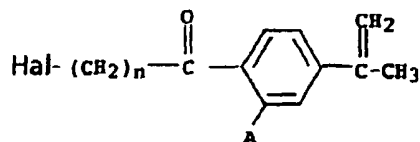
25 wherein

W represents $-\text{C}(=\text{O})-$ or $-\text{CH}(\text{OH})-$;
 R_1 represents hydrogen or hydroxy;
 R_2 represents hydrogen; or
 R_1 and R_2 taken together form a second bond between the
 30 carbon atoms bearing R_1 and R_2 ;
 n is an integer of from 1 to 5;
 m is an integer 0 or 1;
 R_3 is $-\text{COOH}$ or $-\text{COOalkyl}$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;
 35 each of A is hydrogen or hydroxy; and
 pharmaceutically acceptable salts and individual optical isomers thereof, with the proviso that where R_1 and R_2 are taken together to form a second bond between the

-193-

carbon atoms bearing R_1 and R_2 or where R_1 represented hydroxy, m is an integer 0, comprising using an intermediate compound of the formula

5



10 wherein

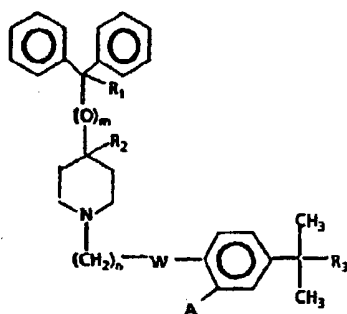
Hal is Cl, Br or I;

n is an integer of from 1 to 5; and

A is a hydrogen or hydroxy.

15 22. A process for preparing a compound of the formula

20



25

wherein

W represents $-C(=O)-$ or $-CH(OH)-$;

R_1 represents hydrogen or hydroxy;

30 R_2 represents hydrogen; or

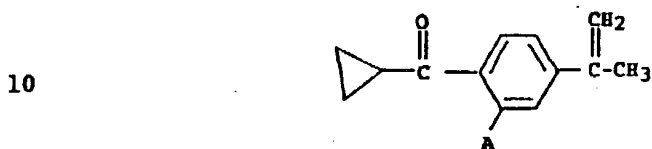
R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;

n is an integer of from 1 to 5;

m is an integer 0 or 1;

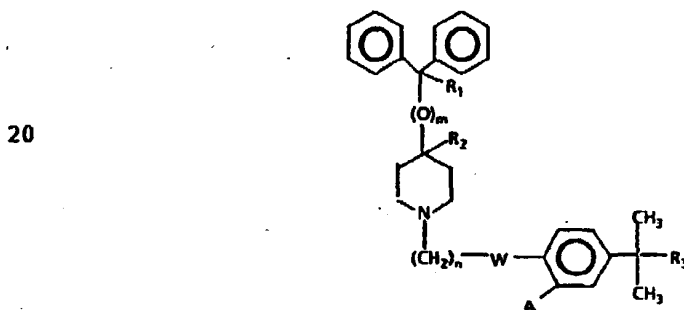
35 R_3 is $-COOH$ or $-COOalkyl$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched; each of A is hydrogen or hydroxy; and

pharmaceutically acceptable salts and individual optical isomers thereof, with the proviso that where R_1 and R_2 are taken together to form a second bond between the carbon atoms bearing R_1 and R_2 or where R_1 represented hydroxy, m is an integer 0, comprising using an intermediate compound of the formula



wherein A is a hydrogen or hydroxy.

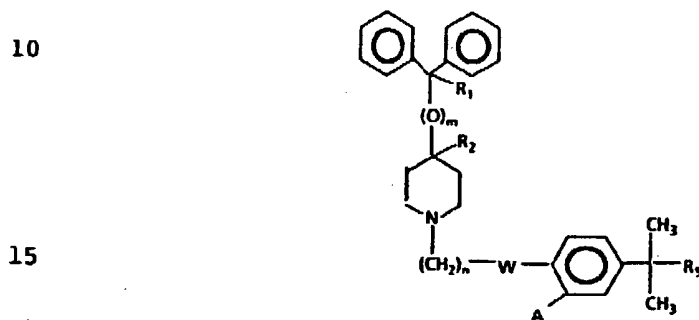
15 23. A process for preparing a compound of the formula



wherein

- W represents $-C(=O)-$ or $-CH(OH)-$;
 R_1 represents hydrogen or hydroxy;
 R_2 represents hydrogen; or
 R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;
 n is an integer of from 1 to 5;
 m is an integer 0 or 1;
 R_3 is $-COOH$ or $-COOalkyl$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;
each of A is hydrogen or hydroxy; and

pharmaceutically acceptable salts and individual optical isomers thereof, with the proviso that where R_1 and R_2 are taken together to form a second bond between the carbon atoms bearing R_1 and R_2 or where R_1 represented hydroxy, m is an integer 0, comprising using an intermediate compound of the formula



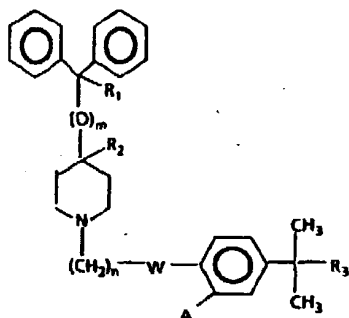
wherein

- 20 W represents $-C(=O)-$ or $-CH(OH)-$;
 R_1 represents hydrogen or hydroxy;
 R_2 represents hydrogen; or
 R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;
 25 n is an integer of from 1 to 5;
 m is an integer 0 or 1;
 R_5 is H, Br, Cl, I, CN or $-CONR_6R_7$ wherein R_6 and R_7 are each independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy or R_6 and R_7 taken together with the nitrogen atom
 30 form a pyrrolidine, piperidine or morpholine, with the proviso that R_6 and R_7 cannot both be represented by C_1-C_6 alkoxy;
 A is hydrogen or hydroxy; and
 pharmaceutically acceptable salts and individual optical
 35 isomers thereof, with the proviso that where R_1 and R_2 are taken together to form a second bond between the carbon atoms bearing R_1 and R_2 or where R_1 represented hydroxy, m is an integer 0.

24. A process for preparing a compound of the formula

5

10



15 wherein

W represents $-C(=O)-$ or $-CH(OH)-$;

R_1 represents hydrogen or hydroxy;

R_2 represents hydrogen; or

R_1 and R_2 taken together form a second bond between the

20

carbon atoms bearing R_1 and R_2 ;

n is an integer of from 1 to 5;

m is an integer 0 or 1;

R_3 is $-COOH$ or $-COOalkyl$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;

25

each of A is hydrogen or hydroxy; and

pharmaceutically acceptable salts and individual optical isomers thereof, with the proviso that where R_1 and R_2 are taken together to form a second bond between the carbon atoms bearing R_1 and R_2 or where R_1 represented

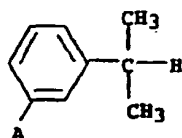
30

hydroxy, m is an integer 0,

comprising the steps of:

(a) reacting a cumene compound of the formula

35



-197-

wherein A is as defined above with a ω -halo compound of the formula



wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of a suitable Lewis acid to produce a ω -halo cumylketone compound;

10

(b) reacting the ω -halo cumylketone compound with a suitable halogenating agent to give a ω -halo-halocumylketone compound;

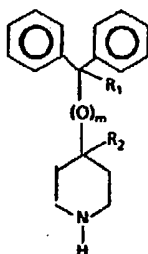
15 (c) reacting the ω -halo-halocumylketone compound with a suitable cyanating agent to give a ω -halo-cyanocumylketone compound;

20 (d) reacting the ω -halo-cyanocumylketone compound with an appropriate straight or branched $\text{C}_1\text{-C}_6$ alcohol in the presence of a suitable anhydrous acid to give a ω' -halo- α' -keto- α,α -dimethylphenylacetic acid imidate compound;

25 (e) reacting the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid imidate compound with water to give a ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound;

30 (f) reacting the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound with a piperidine compound of the formula

35



5

10 wherein R_1 , R_2 and m are as defined above in the presence of a suitable non-nucleophilic base to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOalkyl and W is $-C(=O)-$;

15

(g) optionally hydrolyzing the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOalkyl and W is $-C(=O)-$ to produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH and W is $-C(=O)-$;

20

(h) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOalkyl and W is $-C(=O)-$ or the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH and W is $-C(=O)-$ with a suitable reducing agent to produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOH$ and W is $-CH(OH)-$ or the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOalkyl$ and W is $-CH(OH)-$; and

30

(i) optionally reacting the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOH$ and W is $-CH(OH)-$ or the appropriate ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOH$ and W is $-C(=O)-$ with an appropriate straight or branched C_1 - C_6 alcohol in the presence of a suitable acid to produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOalkyl$ and W is $-$

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-199-

CH(OH)- or a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative wherein R_3 is -COOalkyl and W is -C(=O)-; and

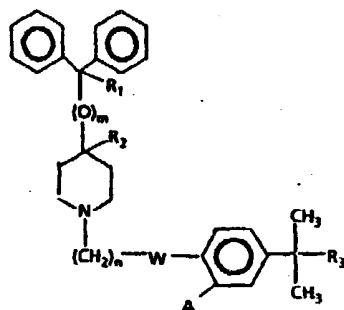
- 5 (j) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOH and W is -C(=O)-, the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOalkyl and W is -C(=O)-, the ω' -piperidine- α' -hydroxy- α,α -
 10 dimethylphenyl derivative of formula (I) wherein R_3 is -COOH and W is -CH(OH)- or the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOalkyl and W is -CH(OH)- with an appropriate deprotecting reagent,

15

with the proviso that each of the hydroxy groups present in the compounds described in steps a-i are optionally protected or unprotected.

- 20 25. A process for preparing a compound of the formula

25



30

wherein

- W represents -C(=O)- or -CH(OH)-;
 R_1 represents hydrogen or hydroxy;
 35 R_2 represents hydrogen; or
 R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;
 n is an integer of from 1 to 5;

-200-

m is an integer 0 or 1;
 R₃ is -COOH or -COOalkyl wherein the alkyl moiety has
 from 1 to 6 carbon atoms and is straight or branched;
 5 each of A is hydrogen or hydroxy; and
 pharmaceutically acceptable salts and individual optical
 isomers thereof, with the proviso that where R₁ and R₂
 are taken together to form a second bond between the
 carbon atoms bearing R₁ and R₂ or where R₁ represented
 10 hydroxy, m is an integer 0, comprising the steps of:

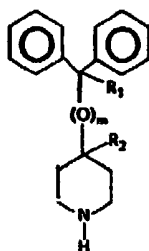
(a) reacting a ω-halo-halocumylketone compound with
 carbon dioxide under electrochemical reduction conditions to
 give a ω'-halo-α'-keto-α,α-dimethylphenylacetic compound;

15 (b) reacting the ω'-halo-α'-keto-α,α-
 dimethylphenylacetic compound compound with an appropriate
 straight or branched C₁-C₆ alcohol in the presence of a
 suitable anhydrous acid to give a ω'-halo-α'-keto-α,α-
 20 dimethylphenylacetic acid ester compound;

(c) reacting the ω'-halo-α'-keto-α,α-
 dimethylphenylacetic acid ester compound with a piperidine
 compound of the formula

25

30



wherein R₁, R₂ and m are as defined above in the presence of
 a suitable non-nucleophilic base to produce a ω'-piperidine-
 35 α'-keto-α,α-dimethylphenyl derivative of formula (I) wherein
 R₃ is COOalkyl and W = -C(=O)-;

(d) optionally hydrolyzing the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOalkyl and W is $-C(=O)-$ to produce a ω' -piperidine- α' -
5 keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH and W is $-C(=O)-$;

(e) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is
10 COOalkyl and W is $-C(=O)-$ or the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH and W is $-C(=O)-$ with a suitable reducing agent to produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of
15 formula (I) wherein R_3 is $-COOH$ and W is $-CH(OH)-$ or the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOalkyl$ and W is $-CH(OH)-$; and

(f) optionally reacting the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-$
20 COOH and W is $-CH(OH)-$ or the appropriate ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOH$ and W is $-C(=O)-$ with an appropriate straight or branched C_1 - C_6 alcohol in the presence of a suitable acid to
25 produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOalkyl$ and W is $-CH(OH)-$ or a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOalkyl$ and W is $-C(=O)-$; and

30 (g) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOH$ and W is $-C(=O)-$, the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOalkyl$ and W is $-C(=O)-$, the ω' -piperidine- α' -hydroxy- α,α -
35 dimethylphenyl derivative of formula (I) wherein R_3 is $-COOH$ and W is $-CH(OH)-$ or the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-$

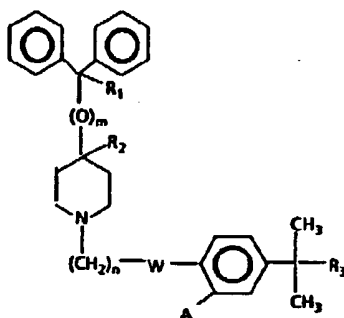
COOalkyl and W is -CH(OH)- with an appropriate deprotecting reagent,

5 with the proviso that each of the hydroxy groups present in the compounds described in steps a-f are optionally protected or unprotected.

26. A process for preparing a compound of the formula

10

15



20

wherein

W represents -C(=O)- or -CH(OH)-;

R1 represents hydrogen or hydroxy;

R2 represents hydrogen; or

25 R1 and R2 taken together form a second bond between the carbon atoms bearing R1 and R2;

n is an integer 3;

m is an integer 0 or 1;

30 R3 is -COOH or -COOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;

each of A is hydrogen or hydroxy; and

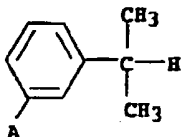
pharmaceutically acceptable salts and individual optical isomers thereof, with the proviso that where R1 and R2

35 are taken together to form a second bond between the carbon atoms bearing R1 and R2 or where R1 represented hydroxy, m is an integer 0, comprising the steps of:

-203-

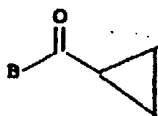
(a) reacting a cumyl compound of the formula

5



wherein A is as defined above with an appropriate cyclopropyl compound of the structure

10



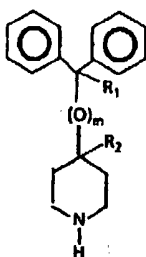
15 wherein B is halo or hydroxy, in the presence of a suitable Lewis acid to produce a cyclopropyl cumylketone compound;

(b) reacting the cyclopropyl cumylketone compound with a suitable halogenating agent to give a cyclopropyl
20 halocumylketone compound;

(c) reacting the cyclopropyl halocumylketone compound with carbon dioxide under electrochemical reduction conditions to give a cyclopropylketo- α,α -
25 dimethylphenylacetic acid compound;

(d) reacting the cyclopropylketo- α,α -dimethylphenylacetic with an appropriate straight or branched C_1 - C_6 alcohol in the presence of a suitable
30 anhydrous acid to give a ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound;

(e) reacting the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound with a piperidine
35 compound of the formula



- 5
- 10 wherein R_1 , R_2 and m are as defined above in the presence of a suitable non-nucleophilic base to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOalkyl and $W = -C(=O)-$;
- 15 (f) optionally hydrolyzing the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOalkyl and W is $-C(=O)-$ to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH and W is $-C(=O)-$;
- 20 (g) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOalkyl and W is $-C(=O)-$ or the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH and W is $-C(=O)-$ with a suitable reducing agent to produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOH$ and W is $-CH(OH)-$ or the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOalkyl$ and W is $-CH(OH)-$; and
- 25 30 (h) optionally reacting the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOH$ and W is $-CH(OH)-$ or the appropriate ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOH$ and W is $-C(=O)-$ with an appropriate straight or branched C_1 - C_6 alcohol in the presence of a suitable acid to produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-COOalkyl$ and W is
- 35

-CH(OH)- or a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOalkyl and W is -C(=O)-; and

- 5
 (i) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOH and W is -C(=O)-, the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -
 10 COOalkyl and W is -C(=O)-, the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOH and W is -CH(OH)- or the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOalkyl and W is -CH(OH)- with an appropriate deprotecting
 15 reagent,

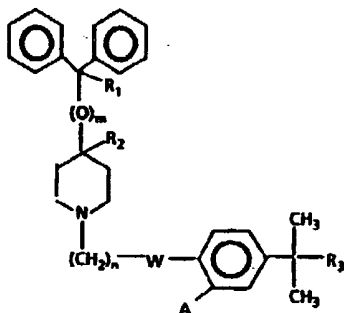
with the proviso that each of the hydroxy groups present in the compounds described in steps a-h are optionally protected or unprotected.

20

27. A process for preparing a compound of the formula

25

30



wherein

- W represents -C(=O)- or -CH(OH)-;
 35 R_1 represents hydrogen or hydroxy;
 R_2 represents hydrogen; or
 R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;

n is an integer of from 1 to 5;

m is an integer 0 or 1;

R₃ is -COOH or -COOalkyl wherein the alkyl moiety has

from 1 to 6 carbon atoms and is straight or branched;

each of A is hydrogen or hydroxy; and

pharmaceutically acceptable salts and individual optical

isomers thereof, with the proviso that where R₁ and R₂

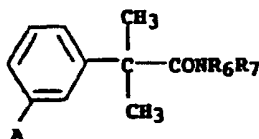
are taken together to form a second bond between the

carbon atoms bearing R₁ and R₂ or where R₁ represented

hydroxy, m is an integer 0, comprising the steps of:

(a) reacting a α,α -dimethylphenylacetic acid amide

compound of the formula



wherein A is as defined above and R₆ and R₇ are each

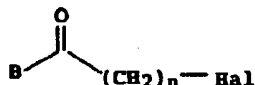
independently H, C₁-C₆alkyl, C₁-C₆alkoxy or R₆ and R₇ taken

together with the nitrogen atom for a pyrrolidine,

piperidine or morpholine, with the proviso that R₆ and R₇

cannot both be represented by C₁-C₆alkoxy with a ω -halo

compound of the formula



wherein B is halo or hydroxy, Hal represents Cl, Br or I and

n is as defined above, in the presence of a suitable Lewis

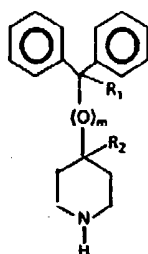
acid to produce a ω' -halo- α' -keto- α,α -dimethylphenylacetic

acid amide compound;

(b) reacting the ω' -halo- α' -keto- α,α -

dimethylphenylacetic acid amide compound with a piperidine

compound of the formula



5

10 wherein R_1 and R_2 are as defined above in the presence of a suitable non-nucleophilic base to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (XI) wherein R_5 is $-\text{CONR}_6\text{R}_7$ wherein R_6 and R_7 are as defined above;

15

(c) optionally hydrolyzing the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (XI) wherein R_5 is $-\text{CONR}_6\text{R}_7$ wherein R_6 and R_7 are as defined above to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of
20 formula (I) wherein R_3 is COOH and W is $-\text{C}(=\text{O})-$;

20

(d) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH and W is $-\text{C}(=\text{O})-$ with a suitable reducing agent to produce a
25 ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-\text{COOH}$ and W is $-\text{CH}(\text{OH})-$; and

25

(e) optionally reacting the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-\text{COOH}$ and W is $-\text{CH}(\text{OH})-$ or the appropriate ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-\text{COOH}$ and W is $-\text{C}(=\text{O})-$ with an appropriate straight or
30 branched C_1 - C_6 alcohol in the presence of a suitable acid to produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl
35 derivative of formula (I) wherein R_3 is $-\text{COOalkyl}$ and W is $-\text{CH}(\text{OH})-$ or a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-\text{COOalkyl}$ and W is $-\text{C}(=\text{O})-$; and

30

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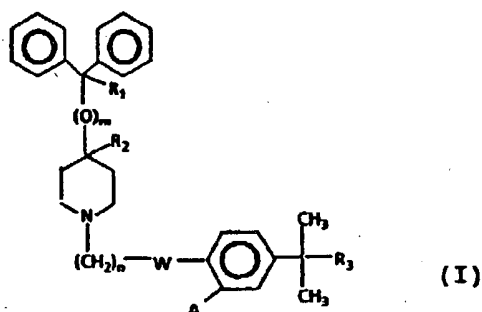
(f) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-\text{COOH}$ 5 and W is $-\text{C}(=\text{O})-$, the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-\text{COOalkyl}$ and W is $-\text{C}(=\text{O})-$, the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-\text{COOH}$ and W is $-\text{CH}(\text{OH})-$ or the ω' -piperidine- α' -hydroxy- α,α - 10 dimethylphenyl derivative of formula (I) wherein R_3 is $-\text{COOalkyl}$ and W is $-\text{CH}(\text{OH})-$ with an appropriate deprotecting reagent,

with the proviso that each of the hydroxy groups present in 15 the compounds described in steps a-e are optionally protected or unprotected.

28. A process for preparing a compound of the formula

20

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30 wherein

W represents $-\text{C}(=\text{O})-$ or $-\text{CH}(\text{OH})-$;

R_1 represents hydrogen or hydroxy;

R_2 represents hydrogen; or

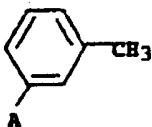
R_1 and R_2 taken together form a second bond between the 35 carbon atoms bearing R_1 and R_2 ;

n is an integer of from 1 to 5;

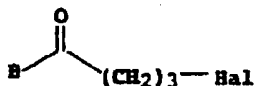
m is an integer 0 or 1;

R_3 is $-\text{COOH}$ or $-\text{COOalkyl}$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched; each of A is hydrogen or hydroxy; and
5 pharmaceutically acceptable salts and individual optical isomers thereof, with the proviso that where R_1 and R_2 are taken together to form a second bond between the carbon atoms bearing R_1 and R_2 or where R_1 represented hydroxy, m is an integer 0, comprising the steps of:

10 (a) reacting a toluene compound of the formula



wherein A is as defined above with a ω -halo compound of the formula



wherein B is halo or hydroxy, Hal represents Cl, Br or I and
25 n is as defined above, in the presence of a suitable Lewis acid to produce a ω -halo-tolylketone compound;

(b) reacting the ω -halo-tolylketone compound with a suitable base to give a cyclopropyl-tolylketone compound;

30 (c) reacting the cyclopropyl-tolylketone compound with a suitable halogenating agent to give a cyclopropyl-halotolylketone compound;

35 (d) reacting the cyclopropyl-halotolylketone compound with a suitable cyanating agent to give a cyclopropyl cyanotolylketone compound;

(e) reacting the cyclopropyl cyanotolylketone compound with a suitable methylating agent to give a cyclopropyl cyanocumylketone compound;

5

(f) reacting the cyclopropyl cyanocumylketone compound with a suitable base to give a cyclopropylketo- α,α -dimethylphenylacetic acid amide;

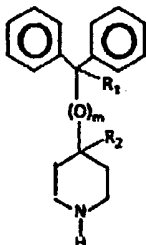
10

(g) reacting the cyclopropylketo- α,α -dimethylphenylacetic acid amide with an appropriate straight or branched C_1-C_6 alcohol in the presence of a suitable anhydrous acid to give a ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound;

15

(h) reacting the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound with a piperidine compound of the formula

20



25

wherein R_1 , R_2 and m are as defined above in the presence of a suitable non-nucleophilic base to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative;

30

(i) optionally hydrolyzing the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $COOH$ and W is $-C(=O)-$;

35

(j) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $COOH$ and W is $-C(=O)-$ with a suitable reducing agent to produce a

-211-

ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-\text{COOH}$ and W is $-\text{CH}(\text{OH})-$; and

- 5 (k) optionally reacting the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-\text{COOH}$ and W is $-\text{CH}(\text{OH})-$ or the appropriate ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-\text{COOH}$ and W is $-\text{C}(=\text{O})-$ with an appropriate straight or
10 branched $\text{C}_1\text{-C}_6$ alcohol in the presence of a suitable acid to produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-\text{COOalkyl}$ and W is $-\text{CH}(\text{OH})-$ or a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (II) wherein R_3 is $-\text{COOalkyl}$ and W is
15 $-\text{C}(=\text{O})-$; and

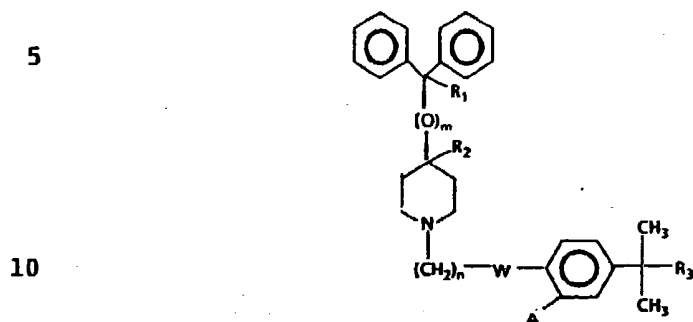
- (l) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (II) wherein R_3 is $-\text{COOH}$ and W is $-\text{C}(=\text{O})-$, the ω' -piperidine- α' -keto- α,α -
20 dimethylphenyl derivative of formula (II) wherein R_3 is $-\text{COOalkyl}$ and W is $-\text{C}(=\text{O})-$, the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-\text{COOH}$ and W is $-\text{CH}(\text{OH})-$ or the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl of formula (I) wherein R_3 is $-\text{COOalkyl}$ and W
25 is $-\text{CH}(\text{OH})-$ with an appropriate deprotecting reagent,

with the proviso that each of the hydroxy groups present in the compounds described in steps a-k are optionally protected or unprotected.

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29. A process for preparing a compound of the formula



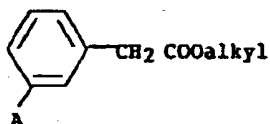
wherein

- 15 W represents $-C(=O)-$ or $-CH(OH)-$;
 R_1 represents hydrogen or hydroxy;
 R_2 represents hydrogen; or
 R_1 and R_2 taken together form a second bond between the
carbon atoms bearing R_1 and R_2 ;
20 n is an integer of from 1 to 5;
m is an integer 0 or 1;
 R_3 is $-COOH$ or $-COOalkyl$ wherein the alkyl moiety has
from 1 to 6 carbon atoms and is straight or branched;
each of A is hydrogen or hydroxy; and
25 pharmaceutically acceptable salts and individual optical
isomers thereof, with the proviso that where R_1 and R_2
are taken together to form a second bond between the
carbon atoms bearing R_1 and R_2 or where R_1 represented
hydroxy, m is an integer 0, comprising the steps of:

30

(a) reacting a phenylacetic acid ester compound of the
formula

35



wherein A is as defined above with a ω -halo compound of the formula



wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of a suitable Lewis acid to produce a ω' -halo- α' -keto-phenylacetic acid ester
10 compound;

(b) reacting the ω' -halo- α' -keto-phenylacetic acid ester compound with a suitable methylating agent in the presence of a suitable base to give a cyclopropylketo- α,α -
15 dimethylphenylacetic acid ester;

(c) purifying the cyclopropylketo- α,α -dimethylphenylacetic acid ester by distillation and/or recrystallization;
20

(d) reacting the cyclopropylketo- α,α -dimethylphenylacetic acid ester with an appropriate straight or branched $\text{C}_1\text{-C}_6$ alcohol in the presence of a suitable anhydrous acid to give a ω' -halo- α' -keto- α,α -
25 dimethylphenylacetic acid ester compound;

(e) reacting the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound with a piperidine compound of the formula
30



wherein R_1 , R_2 and m are as defined above in the presence of a suitable non-nucleophilic base to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOalkyl and W is -C(=O)-;

(f) optionally hydrolyzing the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOalkyl and W is -C(=O)- to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH and W is -C(=O)-;

(g) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH and W is -C(=O)- with a suitable reducing agent to produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOH and W is -CH(OH)-; and

(h) optionally reacting the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOH and W is -CH(OH)- or the appropriate ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOH and W is -C(=O)- with an appropriate straight or branched C_1 - C_6 alcohol in the presence of a suitable acid to produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOalkyl and W is -CH(OH)- or a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOalkyl and W is -C(=O)-; and

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(i) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOH and W is -C(=O)-, the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOalkyl and W is -C(=O)-, the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOH and W is -CH(OH)- or the ω' -piperidine- α' -hydroxy- α,α -

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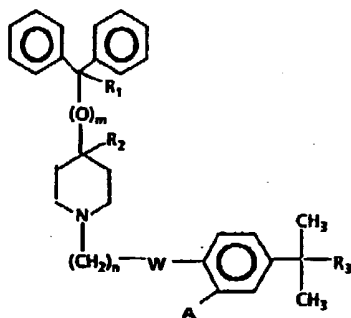
dimethylphenyl of formula (I) wherein R_3 is $-\text{COOalkyl}$ and W is $-\text{CH(OH)}-$ with an appropriate deprotecting reagent,

5 with the proviso that each of the hydroxy groups present in the compounds described in steps a-h are optionally protected or unprotected.

30. A process for preparing a compound of the formula

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wherein

W represents $-\text{C(=O)}-$ or $-\text{CH(OH)}-$;

R_1 represents hydrogen or hydroxy;

R_2 represents hydrogen; or

25 R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;

n is an integer of from 1 to 5;

m is an integer 0 or 1;

30 R_3 is $-\text{COOH}$ or $-\text{COOalkyl}$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;

each of A is hydrogen or hydroxy; and

pharmaceutically acceptable salts and individual optical isomers thereof, with the proviso that where R_1 and R_2 are taken together to form a second bond between the carbon atoms bearing R_1 and R_2 or where R_1 represented hydroxy, m is an integer 0, comprising the steps of:

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-216-

(a) reacting a phenylacetic acid ester compound of the formula



wherein A is as defined above with a suitable methylating agent to give a α,α -dimethylphenylacetic acid ester;

(b) reacting the α,α -dimethylphenylacetic acid ester with a ω -halo compound of the formula

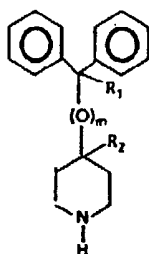


wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is 3, in the presence of a suitable Lewis acid to produce a cyclopropylketo- α,α -dimethylphenylacetic acid ester;

(c) purifying the cyclopropylketo- α,α -dimethylphenylacetic acid ester by distillation and/or recrystallization;

(d) reacting the cyclopropylketo- α,α -dimethylphenylacetic acid ester with an appropriate straight or branched C₁-C₆ alcohol in the presence of a suitable anhydrous acid to give a ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound;

(e) reacting the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid ester compound with a piperidine compound of the formula



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wherein R_1 , R_2 and m are as defined above in the presence of a suitable non-nucleophilic base to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOalkyl and W is -C(=O)-;

15

(f) optionally hydrolyzing the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOalkyl and W is -C(=O)- to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH and W is -C(=O)-;

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(g) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is COOH and W is -C(=O)- with a suitable reducing agent to produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOH and W is -CH(OH)-; and

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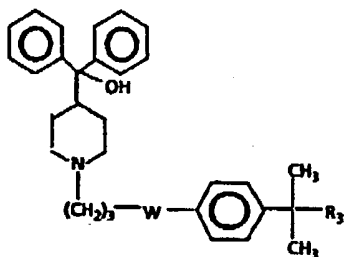
35

(h) optionally reacting the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOH and W is -CH(OH)- or the appropriate ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOH and W is -C(=O)- with an appropriate straight or branched C_1 - C_6 alcohol in the presence of a suitable acid to produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOalkyl and W is -CH(OH)- or a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is -COOalkyl and W is -C(=O)-; and

(i) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-\text{COOH}$ and W is $-\text{C}(=\text{O})-$, the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-\text{COOalkyl}$ and W is $-\text{C}(=\text{O})-$, the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-\text{COOH}$ and W is $-\text{CH}(\text{OH})-$ or the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative of formula (I) wherein R_3 is $-\text{COOalkyl}$ and W is $-\text{CH}(\text{OH})-$ with an appropriate deprotecting reagent,

with the proviso that each of the hydroxy groups present in the compounds described in steps a-h are optionally protected or unprotected.

31. A process for preparing piperidine derivatives of formula



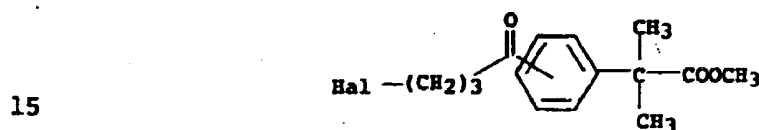
wherein

- W represents $-\text{C}(=\text{O})-$ or $-\text{CH}(\text{OH})-$;
 R_3 is $-\text{COOH}$ or $-\text{COOCH}_3$; and
 pharmaceutically acceptable salts and individual optical isomers thereof, comprising the steps of:
- (a) reacting phenylacetic acid methyl ester with a suitable methylating agent in the presence of a suitable base to give α,α -dimethylphenylacetic acid methyl ester;

(b) reacting α,α -dimethylphenylacetic acid methyl ester with a ω -halo compound of the formula



wherein B is halo or hydroxy and Hal represents Cl, Br or I in the presence of a suitable Lewis acid to produce a mixture of meta and para isomers of ω' -halo- α' -keto- α,α -dimethylphenylacetic acid methyl ester compounds of the formula



wherein Hal is defined above;

(c) separating the para isomer of the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid methyl ester compound by crystallization;

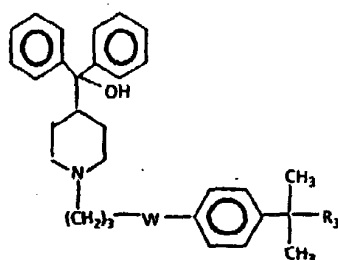
(d) reacting the para isomer of the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid methyl ester compound with a piperidine compound of the formula



in the presence of a suitable non-nucleophilic base to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula

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wherein

W represents $-C(=O)-$;

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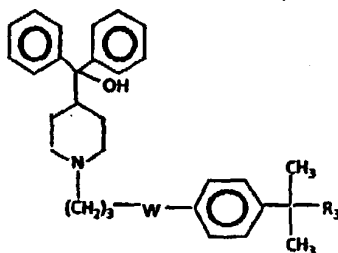
R_3 is $-COOCH_3$; and

pharmaceutically acceptable salts and individual optical isomers thereof;

(e) optionally hydrolyzing the ω' -piperidine- α' -keto-
20 α,α -dimethylphenyl derivative wherein R_3 is $COOCH_3$ and W is $-C(=O)-$ to produce a ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative of formula

25

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wherein

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W represents $-C(=O)-$;

R_3 is $-COOH$; and

pharmaceutically acceptable salts and individual optical isomers thereof;

(f) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative wherein R_3 is COOCH_3 and W is - $\text{C}(=\text{O})$ - or the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative wherein R_3 is COOH and W is - $\text{C}(=\text{O})$ - with a suitable reducing agent to produce a ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative wherein R_3 is - COOH and W is - $\text{CH}(\text{OH})$ - or the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative wherein R_3 is COOCH_3 and W is - $\text{CH}(\text{OH})$ -; and

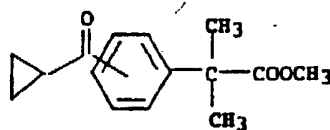
(g) optionally reacting the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative wherein R_3 is - COOH and W is - $\text{C}(=\text{O})$ -, the ω' -piperidine- α' -keto- α,α -dimethylphenyl derivative wherein R_3 is - COOCH_3 and W is - $\text{C}(=\text{O})$ -, the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative wherein R_3 is - COOH and W is - $\text{CH}(\text{OH})$ - or the ω' -piperidine- α' -hydroxy- α,α -dimethylphenyl derivative wherein R_3 is - COOCH_3 and W is - $\text{CH}(\text{OH})$ - with an appropriate deprotecting reagent,

with the proviso that the hydroxy groups present in the compounds described in steps a-f are optionally protected or unprotected.

32. A process according to claim 31 wherein the para isomer of the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid methyl ester compound is further separated from the meta isomer of the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid methyl ester compound by recrystallization of the para isomer of the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid methyl ester compound.

33. A process according to Claim 31 wherein additional para isomer of the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid methyl ester compound is recovered from the mother liquors of the crystallization step (c), comprising the steps of:

(a) reacting the mixture of meta and para isomers of ω' -halo- α' -keto- α,α -dimethylphenylacetic acid methyl ester compounds with a suitable base such as sodium methoxide to
 5 give a mixture of meta and para isomers of a cyclopropyl- α,α -dimethylphenylacetic acid methyl ester of the formula



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(b) enriching the para isomer of the cyclopropyl- α,α -dimethylphenylacetic acid methyl ester by removal of the
 15 meta isomer of the cyclopropyl- α,α -dimethylphenylacetic acid methyl ester by distillation; and

(c) reacting the enriched para isomer of the cyclopropyl- α,α -dimethylphenylacetic acid methyl ester with
 20 a suitable anhydrous acid to give the enriched para isomer of the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid methyl ester compound.

34. A process according to Claim 33 wherein the
 25 enriched para isomer of the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid methyl ester compound is further separated from the meta isomer of the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid methyl ester compound by crystallization of the para isomer of the ω' -halo- α' -keto-
 30 α,α -dimethylphenylacetic acid methyl ester compound.

35. A process according to Claim 34 wherein the para isomer of the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid methyl ester compound is further separated from the meta
 35 isomer of the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid methyl ester compound by recrystallization of the para isomer of the ω' -halo- α' -keto- α,α -dimethylphenylacetic acid methyl ester compound.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 94/05982

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D211/14 C07D211/22 C07D211/46 C07D211/70 C07C49/792
 C07C49/83 C07C49/80 C07C49/825 C07C49/86 C07C49/835
 C07C49/798 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,4 550 116 (J. M. P. SOTO) 29 October 1985 cited in the application see column 11, line 65 see formula VII	7-10, 13, 17-31
X	US,A,4 254 129 (CARR ET. AL.) 3 March 1981 cited in the application see formulae XV, XX, XVII	7-10, 17-31
X	US,A,4 285 958 (CARR ET. AL.) 25 August 1981 cited in the application see formulae VII, IX, XIII	7, 17-31
X	US,A,4 254 130 (CARR ET. AL.) 3 March 1981 cited in the application see formulae VII, IX, XIII	7, 17-31

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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

Date of the actual completion of the international search

2 November 1994

Date of mailing of the international search report

11.11.94

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Authorized officer

Kissler, B

INTERNATIONAL SEARCH REPORT

Internal Application No

PCT/US 94/05982

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claims No.
X	JOURNAL OF MEDICINAL CHEMISTRY., vol.16, no.5, 1973, WASHINGTON US pages 487 - 490 Rovnyak, G.; Diassi, P. A.; Levine, S. D.; Sheehan, J. T. 'Synthesis and antiinflammatory activities of (.alpha.-cyclopropyl-p- tolyl)acetic acid and related compounds' see RN 50664-71-6: Methanone, cyclopropyl(4-ethylphenyl)- ---	2
X	SULFUR LETT., vol.15, no.3, 1992 pages 127 - 133 Roche, Danielle; Chavignon, Olivier; Teulade, Jean Claude; Madesclaire, Michel 'Synthesis of new cyclopropylvinyl sulfones by Peterson olefination' see RN 50664-71-6: Methanone, cyclopropyl(4-ethylphenyl)- see RN 7143-76-2: Methanone, cyclopropyl(4-methylphenyl)- see RN 6952-91-6: Methanone, cyclopropyl[4-(1-methylethyl)phenyl]- ---	1-3
P,X	J. AM. CHEM. SOC. (1994), 116(9), 4087-8 Kimura, Norio; Takamuku, Setsuo 'Mechanistic Evaluation of Dissociative Electron-Transfer and Nucleophilic Substitution Reactions' see RN 155789-58-5: 1-Pentanone, 5-bromo-1-(4-methylphenyl)-, radical ion(1-) see RN 155789-57-4: 1-Pentanone, 5-bromo-1-(4-ethylphenyl)-, radical ion(1-) see RN 155789-53-0: 1-Butanone, 4-bromo-1-(4-methylphenyl)-, radical ion(1-) see RN 155789-52-9: 1-Butanone, 4-bromo-1-(4-ethylphenyl)-, radical ion(1-) ---	8,9
X	HETEROCYCLES (1992), 34(7), 1311-15 Gonzalez, Antonio G.; Barrera, Jaime Bermejo; Yanes Hernandez, Carlos 'A synthesis of 3-(hydroxymethyl)-6-methylbenzofuran' see RN 144219-74-9: Ethanone, 2-bromo-1-(2-hydroxy-4-methylphenyl)- ---	9

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INTERNATIONAL SEARCH REPORT

Intern al Application No

PCT/US 94/05982

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BULL. CHEM. SOC. JPN. (1992), 65(6), 1731-3 Okamoto, Tsuyoshi; Kakinami, Takaaki; Nishimura, Tetsuo; Hermawan, Irwan; Kajigaeshi, Shoji 'Preparation of aromatic iodoacetyl derivatives by direct iodination with a potassium iodide-potassium iodate-sulfuric acid system' see RN 143278-21-1: Ethanone, 1-(4-ethylphenyl)-2-iodo-	8
X	BULL. CHEM. SOC. JPN. (1991), 64(10), 2965-77 'Preparation and reactivities of (.eta.3-1- and 2-trimethylsiloxyallyl)Fe(CO)2NO complexes. Intermediates functioning as equivalents of .beta.- and .alpha.-acyl carbocations and acyl carbanions' see RN 130543-59-8: 1-Propanone, 3-iodo-1-(4-methylphenyl)-	9
X	J. CHEM. SOC., CHEM. COMMUN. (1987), (13), 1028-9 Kalyanam, Nagabushanam; Likhate, M. A. 'Remarkable structural effects in the intramolecularly assisted hydrolysis of aryl chloroalkyl ketones' see RN 113425-32-4: 1-Butanone, 4-chloro-1-(2-hydroxy-4-methylphenyl)-	9
X	EP,A,0 301 421 (BOEHRINGER MANNHEIM G.M.B.H., FED. REP. GER.) 1 February 1989 see RN 107776-20-5: Benzeneacetic acid, 4-(3-chloro-1-oxopropyl)-, ethyl ester	9
X	US,A,4 452 985 (AMERICAN HOME PRODUCTS CORP., USA) 5 June 1984 see RN 92132-57-5: Benzeneacetonitrile, 4-(bromoacetyl)-	9
X	JP,A,58 008 081 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD., JAPAN) 18 January 1983 see RN 85482-45-7: Benzeneacetic acid, 4-(chloroacetyl)-.alpha.-methyl-, methyl ester	8

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 94/05982

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>INDIAN J. CHEM., SECT. B (1982), 21B(6), 602-4</p> <p>Shridhar, D. R.; Sastry, C. V. Reddy; Lal, B.; Singh, P. P.; Rao, C. Seshagiri; Junnarkar, A. Y. 'Antiinflammatory agents. Part VI. Synthesis and antiinflammatory activity of some new 4-(6,8-substituted 2H-1,4-benzoxazin-2-one-3-yl)phenylalkanoic acid esters'</p> <p>see RN 84325-99-5: Benzeneacetic acid, 4-(bromoacetyl)-.alpha.-methyl-, methyl ester</p> <p>see RN 84325-98-4: Benzeneacetic acid, 4-(bromoacetyl)-, methyl ester</p>	8,9
X	<p>PHYSIOL. CHEM. PHYS. (1981), 13(2), 145-52</p> <p>Masuoka, Noriyoshi; Kinuta, Masahiro; Mizuhara, Shunzi 'Color reaction of sugars with cysteine. I. Isolation and chemical structure of a pigment product'</p> <p>see RN 79493-81-5: 1-Propanone, 3-chloro-1-(4-ethyl-2-hydroxyphenyl)-</p>	8
X	<p>CHEM. PHARM. BULL. (1989), 37(4), 958-61</p> <p>Uchida, Minoru; Komatsu, Makoto; Morita, Seiji; Kanbe, Toshimi; Yamasaki, Katsuya; Nakagawa, Kazuyuki 'Studies on gastric antiulcer active agents. III. Synthesis of 1-substituted 4-(5-tetrazolyl)thio-1-butanones and related compounds'</p> <p>see RN 71526-83-5: 1-Butanone, 4-chloro-1-(4-ethylphenyl)-</p>	8
X	<p>SYNTHESIS (1981), (10), 828-9</p> <p>Madesclaire, Michel; Roche, Danielle; Chatonier, Denise; Boucherle, Andre 'One-step synthesis of 2-cyclopropyl-2-hydroxyalkyl methyl sulfoxides by cyclization of 3-chloropropyl ketones in the presence of dimethylsodium'</p> <p>see RN 70289-38-2: 1-Butanone, 4-chloro-1-[4-(1-methylethyl)phenyl]-</p>	7
X	<p>JP,A,52 087 193 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD., JAPAN) 20 July 1977</p> <p>see RN 65330-82-7: Benzeneacetonitrile, 4-(chloroacetyl)-.alpha.-methyl-</p>	8
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INTERNATIONAL SEARCH REPORT

Intern: 1st Application No

PCT/US 94/05982

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BULL. HAFKINE INST. (1977), 5(1), 20-2 Colah, B. R.; Sabnis, S. S.; Vaidya, Nirmala D.; Bhide, M. B. 'Antiinflammatory agents - III. Synthesis of thiazolyl derivatives of possible therapeutic value' see RN 63382-09-2: Benzeneacetic acid, 4-(chloroacetyl)- ---	9
X	JP,A,60 115 547 (NISSAN CHEMICAL INDUSTRIES, LTD., JAPAN) 22 June 1985 see RN 62546-51-4: Ethanone, 2-bromo-1-[4-(bromomethyl)phenyl]- ---	9
X	DE,A,24 32 410 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD) 30 January 1975 see RN 55844-34-3: Benzeneacetonitrile, 4-(chloroacetyl)- see RN 55844-33-2: Benzeneacetic acid, 4-(chloroacetyl)-.alpha.-methyl-, ethyl ester ---	8,9
X	DE,A,30 10 752 (KYOWA HAKKO KOGYO CO., LTD., JAPAN) 2 October 1980 see RN 55453-49-1: Benzeneacetic acid, 4-(bromoacetyl)-, ethyl ester ---	9
X	J. HETEROCYCL. CHEM. (1988), 25(1), 129-37 Sundberg, Richard J.; Dahlhausen, D. J.; Manikumar, G.; Mavunkel, B.; Biswas, Atanu; Srinivasan, V.; King, Fred, Jr.; Waid, Philip 'Preparation of 2-aryl- and 2-(aryloxymethyl)imidazo[1,2-a]pyridines and related compounds' see RN 51012-62-5: Ethanone, 2-bromo-1-[4-(1-methylethyl)phenyl]- ---	7
X	J. CHEM. RES. (S) (1978), (5), 155 Toke, Laszlo; Petnehazy, Imre; Szakal, Gyongyi 'Reactions of trialkyl phosphites with .alpha.-halo ketones. Mechanism of the Perkow and Arbusov reactions' see RN 50690-09-0: Ethanone, 2-chloro-1-(4-ethylphenyl)- see RN 2632-14-6: Ethanone, 2-bromo-1-(4-ethylphenyl)- ---	8
X	SYNTHESIS (1988), (12), 980-1 Boyer, Joseph H.; Natesh, Anbazhagan 'Oxidative assistance in the conversion of .alpha.-iodo ketones to .alpha.-ketols' see RN 40805-62-7: Ethanone, 2-iodo-1-(4-methylphenyl)- ---	9

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INTERNATIONAL SEARCH REPORT

Intern al Application No

PCT/US 94/05982

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE,A,37 30 718 (BASF) 23 March 1989 see RN 38425-26-2: 1-Butanone, 4-chloro-1-(4-methylphenyl)-	9
X	BULL. SOC. CHIM. FR. (1971), (8), 3064-70 Schaal, Catherine '2-Aryltietanes. I. Synthesis. Extension of linear free enthalpy relations to NMR parameters' see RN 33994-09-1: 1-Propanone, 3-bromo-1-(4-methylphenyl)- see RN 33994-10-4: Propiophenone, 3-bromo-4'-ethyl-	9
X	SUOM. KEMISTILEHTI B (1970), 43(2), 91-7 Ruotsalainen, Heikki; Kumpulainen, Leo A.; Virtanen, P. Olavi I. 'Aluminum chloride catalyzed reactions of 3-chloropropionyl chloride with monoalkylbenzenes and biphenyl and the influence of 4'-alkyl and 4'-phenyl substituents on the acid-catalyzed methanolysis of 2-phenyloxetane' see RN 28547-35-5: Benzyl alcohol, .alpha.-(2-chloroethyl)-p-isopropyl- see RN 28547-32-2: 1-Propanone, 3-chloro-1-[4-(1-methylethyl)phenyl]- see RN 28547-31-1: 1-Propanone, 3-chloro-1-(4-ethylphenyl)-	7,8,10
X	BULL. SOC. CHIM. FR. (1984), (7-8, PT. 2), 285-91 Khalaf, Ali A.; Abdel-Wahab, Aboel Magd A.; El-Khawaga, Ahmed M.; El-Zohry, Maher F. 'Modern Friedel-Crafts chemistry. XIII. Intra- and intermolecular cyclization of some carbonyl derivatives under Friedel-Crafts conditions' see RN 22422-21-5: 1-Propanone, 3-chloro-1-(4-methylphenyl)-	9
X	BULL. SOC. CHIM. BELG. (1968), 77(3-4), 149-52 Heidbuchel, P. W. 'Ethanolysis of ortho-, meta-, and para-substituted phenylacetyl chlorides' see RN 21886-60-2: Ethanone, 2-chloro-1-[4-(1-methylethyl)phenyl]-	7
X	TETRAHEDRON LETT. (1968), (33), 3683-4 Bohlmann, F.; Zdero, C 'Abnormal Grignard reaction' see RN 20834-75-7: Ethanone, 2-chloro-1-(2-hydroxy-4-methylphenyl)-	9

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 94/05982

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE,A,26 53 635 (IMPERIAL CHEMICAL INDUSTRIES LTD., ENGL.) 2 June 1977 see RN 7706-78-7: Benzeneacetic acid, 4-(chloroacetyl)-, ethyl ester	9
X	INDIAN J. CHEM., SECT. B (1983), 22B(3), 297-9 Shridhar, D. R.; Sastry, C. V. Reddy; Bansal, O. P.; Rao, P. Pulla 'Antiinflammatory agents. Part VIII. Synthesis of some 3-aryl-2H-1,4-benzoxazine-6-alkanoic acids and methyl 4-(6-chloro-/6-nitro-/2H-1,4-benzoxazin-3-yl)phenylacetates' see RN 7706-77-6: Benzeneacetic acid, 4-(chloroacetyl)-, methyl ester	9
X	SYNTH. COMMUN. (1990), 20(11), 1625-29 Kim, Hak Jin; Kim, Hyoung Rae; Ryu, Eung K. 'One-pot synthesis of .alpha.-chloro ketones from secondary benzylic alcohols using m-chloroperbenzoic acid/HCl/DMF system' see RN 4209-24-9: Ethanone, 2-chloro-1-(4-methylphenyl)-	9
X	J. LABELLED COMPD. RADIOPHARM. (1990), 28(8), 877-99 McPherson, D. W.; Umbricht, G.; Knapp, F. F., Jr. 'Radiolabeling of protein with radioisotopes of copper using p-carboxyalkylphenylglyoxal bis-(4N-methylthiosemicarbazone) (TSC) bifunctional chelates' see RN 3645-67-8: Benzeneacetic acid, 4-(bromoacetyl)-	9
X	J. HETEROCYCL. CHEM. (1988), 25(5), 1471-4 Kane, John M.; Stewart, Kenneth T 'The reactions of thiosemicarbazides and 5-halovalerophenones' see RN 945-96-0: 1-Pentanone, 5-chloro-1-(4-methylphenyl)-	9
P,X	EP,A,0 571 253 (ADIR ET CIE) 24 November 1993 see RN 619-41-0: Ethanone, 2-bromo-1-(4-methylphenyl)-	9

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

I national application No.

PCT/US 94/05982

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims searched incompletely: 7 - 10 ./.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

Lack of conciseness

The definition of the following substituent(s) is too general and/or encompasses too broad a range of totally different chemical groups, only partly supported by examples given in the descriptive part of the application:

R5 , HAL

The number of theoretically conceivable compounds resulting from the combination of all claimed substituents of above list precludes a comprehensive search. Guided by the spirit of the application and the inventive concept as disclosed in the descriptive part of the present application the search has been limited to the following case(s):

1-(.omega.-halo-substituted acyl)-4-X-subst. benzenes
where X is:

Me/Et/i-Pr/2-propenyl-2/CH₂-Hal,CN,Q-C=Q (Q is a hetero atom)/

CHMe-Hal,CN,Q-C=Q (Q is a hetero atom),CMe₂-Hal,CN,Q-C=Q (Q is a hetero atom)

(Cf. Arts. 8, 15 and Rule 33 PCT, Guidelines Exam. Part B, Chapt. III, 3.6, 3.7)

Despite the above limitation(s) the search revealed too many relevant documents and/or compounds so that the search report shall not be considered complete.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 94/05982

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4550116	29-10-85	AU-B- 565293	10-09-87
		AU-A- 3146584	14-02-85
		CA-A- 1264324	09-01-90
		DE-A- 3466982	03-12-87
		EG-A- 16936	28-02-94
		EP-A, B 0134124	13-03-85
		JP-C- 1744429	25-03-93
		JP-B- 4032821	01-06-92
		JP-A- 60094962	28-05-85
US-A-4254129	03-03-81	AT-B- 376208	25-10-84
		AU-B- 531146	11-08-83
		AU-A- 5501680	16-10-80
		BE-A- 882703	31-07-80
		CA-A- 1123438	11-05-82
		CH-A- 643245	30-05-84
		DE-A, C 3007498	23-10-80
		FR-A, B 2453854	07-11-80
		GB-A, B 2048258	10-12-80
		JP-B- 1032823	10-07-89
		JP-C- 1555761	23-04-90
		JP-A- 55141469	05-11-80
		NL-A, B, C 8000754	14-10-80
		SE-B- 448726	16-03-87
		SE-A- 8002634	11-10-80
		US-A- 4285957	25-08-81
US-A-4285958	25-08-81	US-A- 4254130	03-03-81
		AT-B- 376207	25-10-84
		AU-B- 536463	10-05-84
		AU-A- 5501880	16-10-80
		BE-A- 882704	31-07-80
		CA-A- 1123439	11-05-82
		CH-A- 648019	28-02-85
		DE-A, C 3005948	30-10-80
		FR-A, B 2453853	07-11-80
		GB-A, B 2048258	10-12-80
		JP-A- 55139360	31-10-80
		NL-A, B, C 8000762	14-10-80
		SE-B- 448727	16-03-87

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 94/05982

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4285958		SE-A- 8002635	11-10-80
US-A-4254130	03-03-81	AT-B- 376207	25-10-84
		AU-B- 536463	10-05-84
		AU-A- 5501880	16-10-80
		BE-A- 882704	31-07-80
		CA-A- 1123439	11-05-82
		CH-A- 648019	28-02-85
		DE-A, C 3005948	30-10-80
		FR-A, B 2453853	07-11-80
		GB-A, B 2048258	10-12-80
		JP-A- 55139360	31-10-80
		NL-A, B, C 8000762	14-10-80
		SE-B- 448727	16-03-87
		SE-A- 8002635	11-10-80
		US-A- 4285958	25-08-81
EP-A-0301421	01-02-89	DE-A- 3724923	09-02-89
		AU-A- 2015088	02-02-89
		DE-A- 3864474	02-10-91
		JP-A- 1047758	22-02-89
US-A-4452985	05-06-84	NONE	
JP-A-58008081	18-01-83	NONE	
JP-A-52087193	20-07-77	JP-C- 1206818	11-05-84
		JP-B- 58035519	03-08-83
JP-A-60115547	22-06-85	NONE	
DE-A-2432410	30-01-75	JP-C- 959030	14-06-79
		JP-A- 50140477	11-11-75
		JP-B- 53041678	06-11-78
		JP-C- 1152754	30-06-83
		JP-A- 50129585	13-10-75
		JP-B- 57045237	27-09-82
		JP-C- 897567	25-02-78
		JP-A- 50025588	18-03-75
		JP-B- 52021509	10-06-77

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 94/05982

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A-2432410		JP-C- 892534	24-12-77
		JP-A- 50032194	28-03-75
		JP-B- 52017039	12-05-77
		JP-C- 1119803	28-10-82
		JP-A- 50053388	12-05-75
		JP-B- 57011913	08-03-82
		AT-B- 335448	10-03-77
		AU-A- 7088474	08-01-76
		BE-A- 817247	04-11-74
		BE-A- 888695	28-08-81
		CA-A- 1028327	21-03-78
		FR-A,B 2235675	31-01-75
		GB-A- 1442707	14-07-76
		NL-A- 7409124	09-01-75
		SE-B- 416303	15-12-80
		US-A- 3978071	31-08-76
		SE-A- 7408886	08-01-75
		AT-B- 347450	27-12-78
		CH-A- 601296	14-07-78
DE-A-3010752	02-10-80	JP-C- 1407664	27-10-87
		JP-A- 55124742	26-09-80
		JP-B- 62015062	06-04-87
		CH-A- 643809	29-06-84
		FR-A,B 2451910	17-10-80
		GB-A,B 2046259	12-11-80
		US-A- 4381398	26-04-83
		US-A- 4450115	22-05-84
DE-A-3730718	23-03-89	CA-A- 1331608	23-08-94
		DE-A- 3869886	14-05-92
		EP-A,B 0307814	22-03-89
		JP-A- 1071881	16-03-89
		US-A- 5214047	25-05-93
DE-A-2653635	02-06-77	GB-A- 1559977	30-01-80
		AT-B- 349453	10-04-79
		AT-B- 348993	12-03-79
		AU-B- 503657	13-09-79
		AU-A- 1962576	25-05-78

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 94/05982

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A-2653635		BE-A- 848707	24-05-77
		CA-A- 1068695	24-12-79
		CH-A- 624383	31-07-81
		FR-A, B 2332747	24-06-77
		JP-C- 1355565	24-12-86
		JP-A- 52065240	30-05-77
		JP-B- 61020538	22-05-86
		JP-C- 1509559	26-07-89
		JP-A- 61158922	18-07-86
		JP-B- 63060004	22-11-88
		LU-A- 76251	13-12-77
		NL-A- 7613081	27-05-77
		SE-A- 7613079	26-05-77
		US-A- 4105790	08-08-78
EP-A-0571253	24-11-93	FR-A- 2691462	26-11-93
		FR-A- 2694293	04-02-94
		AU-B- 3860893	25-11-93
		JP-A- 6087859	29-03-94

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